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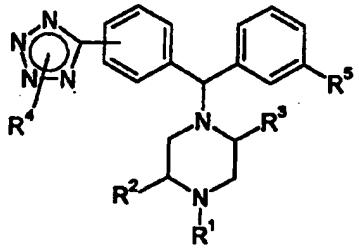
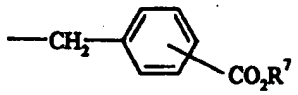


(I)



(a)

(57) Abstract

Tetrazoles and their pharmaceutically acceptable salts which are selective agonists for the delta opioid receptor, particularly useful in the treatment of inflammatory diseases such as arthritis, psoriasis, asthma, inflammatory bowel disease, disorders of respiratory function, gastro-intestinal disorders such as functional bowel disease and functional GI disorders, of formula (I), wherein R^1 is H, C_2–C_6 alkanoyl, C_1–C_6 alkyl, C_2–C_6 alkenyl, C_2–C_6 alkynyl, C_3–C_7 cycloalkyl, (C_3–C_7 cycloalkyl)–(C_1–C_4 alkyl), (C_1–C_4 alkoxy)–(C_1–C_4 alkyl), carboxy–(C_1–C_4 alkyl), aryl–(C_1–C_4 alkyl) or heteroaryl–(C_1–C_4 alkyl); R^2 and R^3 are each independently H or C_1–C_4 alkyl; R^4 is selected from (i) H, (ii) a group of the formula R^6–$(CH_2)_m$–Z–$(CH_2)_n$–, where m is 0, 1, 2 or 3, n is 1, 2 or 3, Z is a direct link or O, and R^6 is –CO_2H or –CO_2(C_1–C_4 alkyl), and (iii) a group of formula (a) where R^7 is H or C_1–C_4 alkyl; and R^5 is hydroxy, C_1–C_4 alkoxy or –$NHSO_2$(C_1–C_4 alkyl); with the proviso that when Z is O, m is 1, 2, or 3 and n is 2 or 3.

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ANTI-INFLAMMATORY PIPERAZINYL-BENZYL-TETRAZOLE DERIVATIVES AND INTERMEDIATES THEREOF

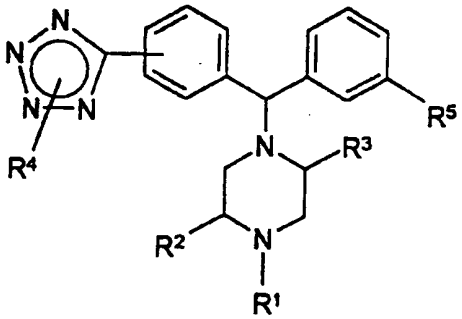
This invention relates to tetrazole derivatives which have utility as ligands for opioid receptors.

More particularly, this invention relates to tetrazoles, their preparation and their use as selective agonists for the *delta* receptor.

At least three subtypes of opioid receptors (*mu*, *delta* and *kappa*) are described and documented in the scientific literature. All three receptors are to be present in the central and peripheral nervous systems of many species including man. Activation of delta receptors is known to produce antinociception in rodents and can induce analgesia in man, in addition to influencing motility of the gastrointestinal tract [see Burks, T.F. (1995) in "The pharmacology of opioid peptides", Tseng L.F. ed. Harwood Academic Publishers].

We have discovered a novel class of tetrazole derivatives which are potent and selective delta opioid agonists which are useful for preventing or treating inflammatory diseases such as arthritis, psoriasis, asthma, or inflammatory bowel disease, disorders of respiratory function, gastro-intestinal disorders such as functional bowel disease, functional GI disorders such as irritable bowel syndrome, functional diarrhoea, functional distension, functional pain, non-ulcerogenic dyspepsia or others associated with disorders of motility or secretion, urogenital tract disorders such as incontinence, as analgesics for treating pain including non-somatic pain, or as immunosuppressants to prevent rejection in organ transplant and skin graft.

Thus the invention provides compounds of the formula:-



---- (I)

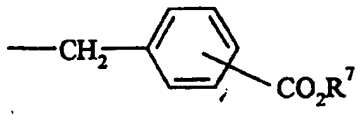
and their pharmaceutically acceptable salts;

wherein

R^1 is H, C_2-C_6 alkanoyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)-(C_1-C_4 alkyl), (C_1-C_4 alkoxy)-(C_1-C_4 alkyl), carboxy-(C_1-C_4 alkyl), aryl-(C_1-C_4 alkyl) or heteroaryl-(C_1-C_4 alkyl);

R^2 and R^3 are each independently H or C_1-C_4 alkyl;

R^4 is selected from (i) H, (ii) a group of the formula R^6-$(CH_2)_m$-Z-$(CH_2)_n$-, where m is 0, 1, 2 or 3, n is 1, 2 or 3, Z is a direct link or O, and R^6 is -CO_2H or -CO_2(C_1-C_4 alkyl), and (iii) a group of the formula



where R^7 is H or C_1-C_4 alkyl;

and R^5 is hydroxy, C_1-C_4 alkoxy or -$NHSO_2$(C_1-C_4 alkyl);

with the proviso that when Z is O, m is 1, 2 or 3 and n is 2 or 3.

Where appropriate, the alkyl, alkanoyl, alkoxy, alkenyl and alkynyl groups can be straight or branched chain.

Preferred aryl groups are phenyl and naphthyl, both optionally substituted by up to three substituents each independently selected from halo, trifluoromethyl, C_1-C_4 alkyl and C_1-C_4 alkoxy.

More preferably, "aryl" is phenyl optionally substituted by one or two substituents as defined above.

"Halo" means F, Cl, Br or I.

Preferred heteroaryl groups include 5- or 6-membered aromatic heterocyclic groups such as thiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl and pyrazolyl.

Thiazol-2-yl is the most preferred heteroaryl group.

The preferred alkyl groups are methyl and ethyl. The preferred alkoxy groups are methoxy and ethoxy. The preferred alkanoyl group is acetyl. The preferred alkenyl

group is allyl. The preferred alkynyl group is vinyl. The preferred cycloalkyl group is cyclopropyl.

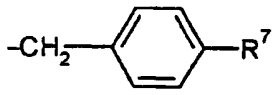
The tetrazole group is preferably attached to the 3- or 4- position of the adjacent phenyl ring.

R^1 is preferably H, allyl, benzyl, C_1-C_4 alkyl, or (C_3-C_7 cycloalkyl)methyl; most preferably allyl.

R^2 and R^3 are preferably each independently H or methyl; more preferably both methyl or both H; most preferably both methyl.

R^5 is preferably hydroxy, methoxy or $-NHSO_2Me$; most preferably hydroxy.

R^4 is preferably H or a group of the formula (a) $-(CH_2)_pCO_2H$ or $-(CH_2)_pCO_2$ (C_1-C_4 alkyl) where p is 1,2,3 or 4, (b) $-(CH_2)_2-O-CH_2CO_2H$, (c) $-(CH_2)_2-O-CH_2CO_2$(C_1-C_4 alkyl) or (d);

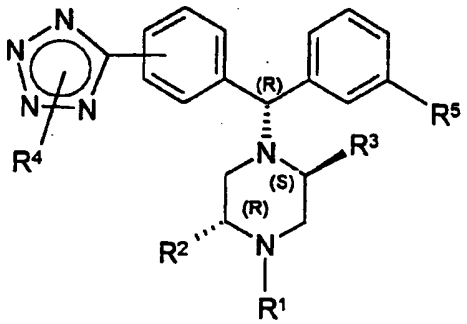


where R^7 is H or C_1-C_4 alkyl.

In R^4, the preferred alkyl group is ethyl.

Preferred individual compounds are those of Examples 1, 4, 24, 27, 36, 42, 94,96,104 and 107.

The preferred stereochemistry of the compounds of the formula (i) is as follows:-



---(IA)

Such compounds are most readily prepared by using starting materials with the appropriate stereochemistry.

The compounds of the formula (I) can be prepared by conventional routes such as those set out in the following Examples and Preparations and in WO-A-9315062.

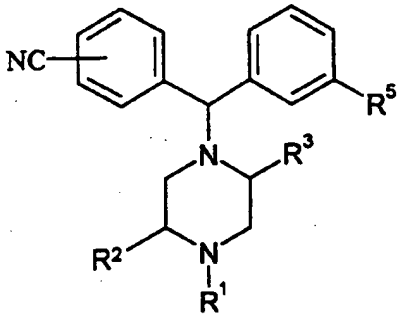
Route A

Compounds of the formula (I) in which R^5 is hydroxy can be prepared by the reaction of the corresponding methoxy compounds of the formula (I) with boron tribromide. Preferably boron tribromide in dichloromethane is added to a solution of the methoxy starting material in dichloromethane and the mixture is stirred at room temperature for a few hours. The product can then be isolated and purified by conventional techniques.

Removal of a hydroxy-protecting group from the corresponding hydroxy-protected compound is also possible, typified by the conversion of t-butyldimethylsilyloxy to hydroxy using tetraethylammonium fluoride.

Route B

The compounds (I) in which R^4 is H, can be prepared by the reaction of a corresponding nitrile of the formula:-



—(II)

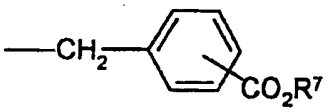
where R^1, R^2, R^3 and R^5 are as defined for formula (I),

with dibutyltin oxide and trimethylsilyl azide.

The reaction is typically carried out in a suitable organic solvent such as dry toluene at from about 50°C to the reflux temperature. If necessary, a hydroxy group represented by R^5 can be protected prior to reaction, e.g. by a t-butyldimethylsilyl protecting group, and the protecting group can be removed subsequently by a conventional technique.

Route C

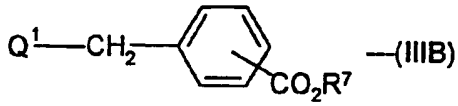
Compounds (I) in which R^4 is either (i) R^6 -$(CH_2)_m$-Z-$(CH_2)_n$- where R^6 is -CO_2(C_1-C_4 alkyl) and Z, m and n are as defined for formula (I) or (ii)



where R^7 is C_1-C_4 alkyl can be prepared by the alkylation of the corresponding compounds in which R^4 is H with an alkylating agent of the formula, respectively, :-

$$R^6\text{-}(CH_2)_m\text{-}Z\text{-}(CH_2)_n\text{-}Q^1 \qquad \text{--- (IIIA)}$$

or



where Z, m and n are as defined for formula (I), R^6 and R^7 are defined in this method and Q^1 is a leaving group, preferably Br.

The reaction is typically carried out in the presence of a base such as potassium or cesium carbonate in a suitable organic solvent, e.g. acetonitrile, under gentle reflux.

This reaction generally produces a mixture of compounds in which the group R^4 is attached to the 1- and 2- positions of the tetrazole ring.

When a compound in which R^5 is hydroxy is required, it may be necessary to protect the hydroxy group before reaction, such as by a t-butyldimethylsilyl group, which can be removed conventionally after reaction, e.g. by the use of tetraethylammonium fluoride.

In an alternative alkylation procedure, the corresponding compound in which R^4 is H is reacted firstly with a strong base such as sodium ethoxide (prepared by adding sodium metal to ethanol) and then with the compound III, no additional base being necessary.

Route D

Compounds (I) in which R^6 is $-CO_2H$ can also be prepared by the hydrolysis, preferably alkaline hydrolysis, of the corresponding esters in which R^6 is C_1-C_4 alkyl.

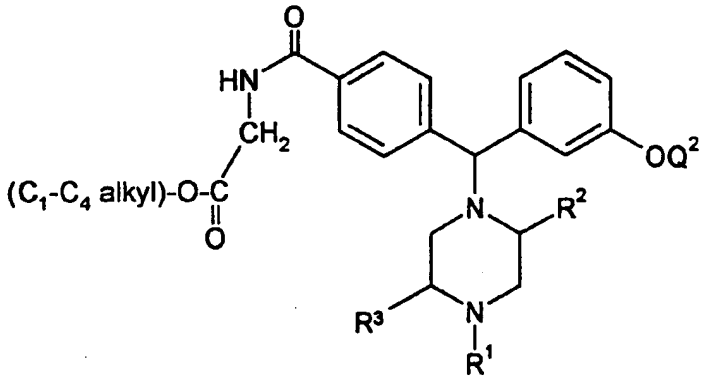
The reaction is typically carried out with aqueous sodium hydroxide in methanol or a mixture of dioxane and methanol at room temperature.

Route E

Compounds (I) in which R^6 is $-CO_2H$ can also be prepared by the hydrolysis of the corresponding compounds in which R^4 is $NC-(CH_2)_m-Z-(CH_2)_n-$
where Z, m and n are as defined for formula (I).
Acidic hydrolysis using hydrogen chloride gas in ethanol is preferred.

Route F

Compounds (I) in which R^4 is 1-[$CH_2CO_2(C_1$-C_4 alkyl)] and R^5 is -OH can be prepared by ring closure by the reaction of a compound of the formula:-

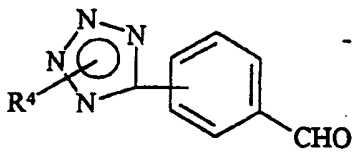


---(IV)

where R^1, R^2 and R^3 are as defined for formula (I) and Q^2 is a hydroxy-protecting group such as t-butyldimethylsilyl, with diethyl azidodicarboxylate, triphenyl phosphine and trimethylsilyl azide in a suitable organic solvent such as toluene.
Generally the protecting group Q^2 is removed under the reaction conditions.

Route G

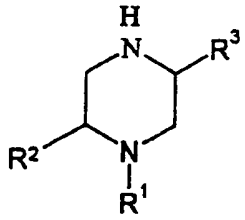
Compounds (I) can be prepared by reaction of an aldehyde of the formula:-



---(V)

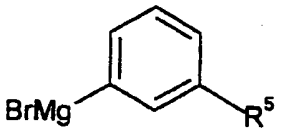
where R^4 is as defined for formula (I),

with a compound of the formula :-



where R^1, R^2 and R^3 are as defined for formula (I),

in the presence of benzotriazole, typically under reflux in an organic solvent such as toluene with azeotropic removal of water, following by cooling, e.g. to -20°C, and reaction with a Grignard reagent of the formula:-



---(VI)

where R^5 is $-OQ^2$ where Q^2 is a hydroxy-protecting group such as trimethylsilyl.

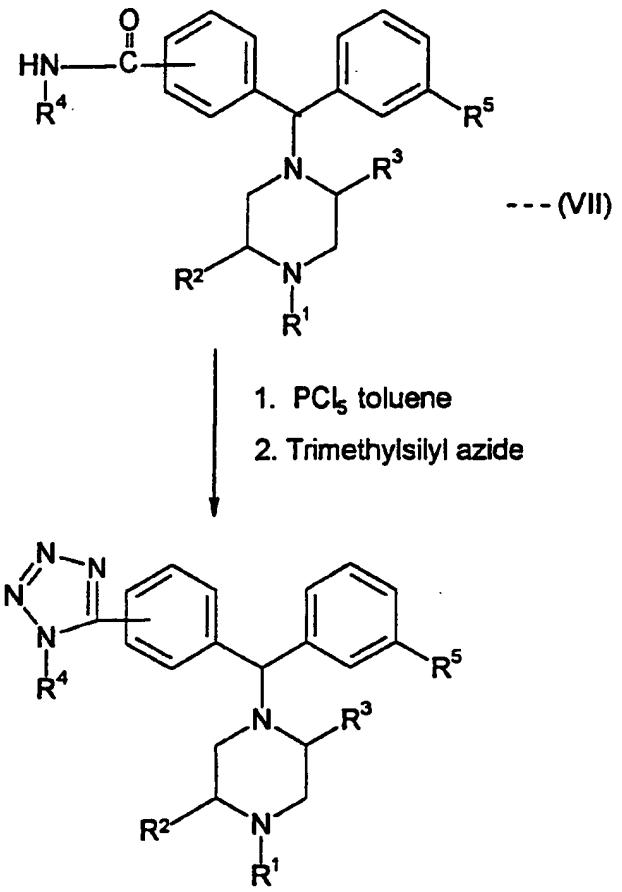
Any hydroxy-protecting groups which are present are generally removed by the reaction conditions, or can be subsequently removed by a conventional technique.

Route H

Compounds in which R^1 is H can be prepared by reaction of the corresponding compound in which R^1 is allyl with tris(triphenylphosphine)rhodium(I) chloride, typically under gentle reflux in a solvent system such as aqueous acetonitrile.

Route I

Compounds of the formula (I) in which R^4 is R^6-$(CH_2)_m$-Z-$(CH_2)_n$- attached to the 1-position of the tetrazole ring and Z,m,n,R^1,R^2,R^3,R^5 and R^6 are as defined for formula (I) can be prepared as follows:-



Route J

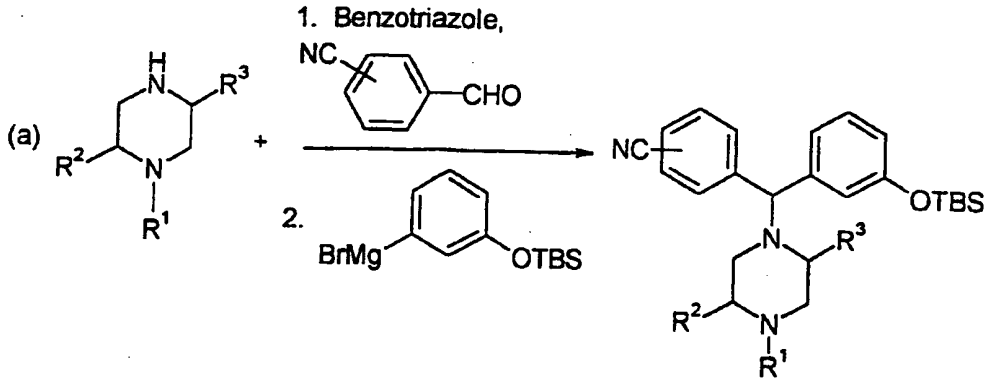
Compounds of the formula (I) in which R^5 is -$NHSO_2$(C_1-C_4 alkyl) can be prepared by the reaction of the corresponding amino-substituted compound with a C_1-C_4 alkanesulphonyl chloride, typically in the presence of an acid-acceptor.

Route K

Compounds of the formula (I) in which R^1 is C_2-C_6 alkyl, aryl –(C_1-C_4 alkyl) or heteroaryl –(C_1-C_4 alkyl) can be prepared by the reductive alkylation of the corresponding compounds in which R^1 is H using the appropriate aldehyde (C_1-C_5 alkyl)CHO, aryl.CHO or heteroaryl.CHO and a reducing agent such as sodium triacetoxyborohydride.

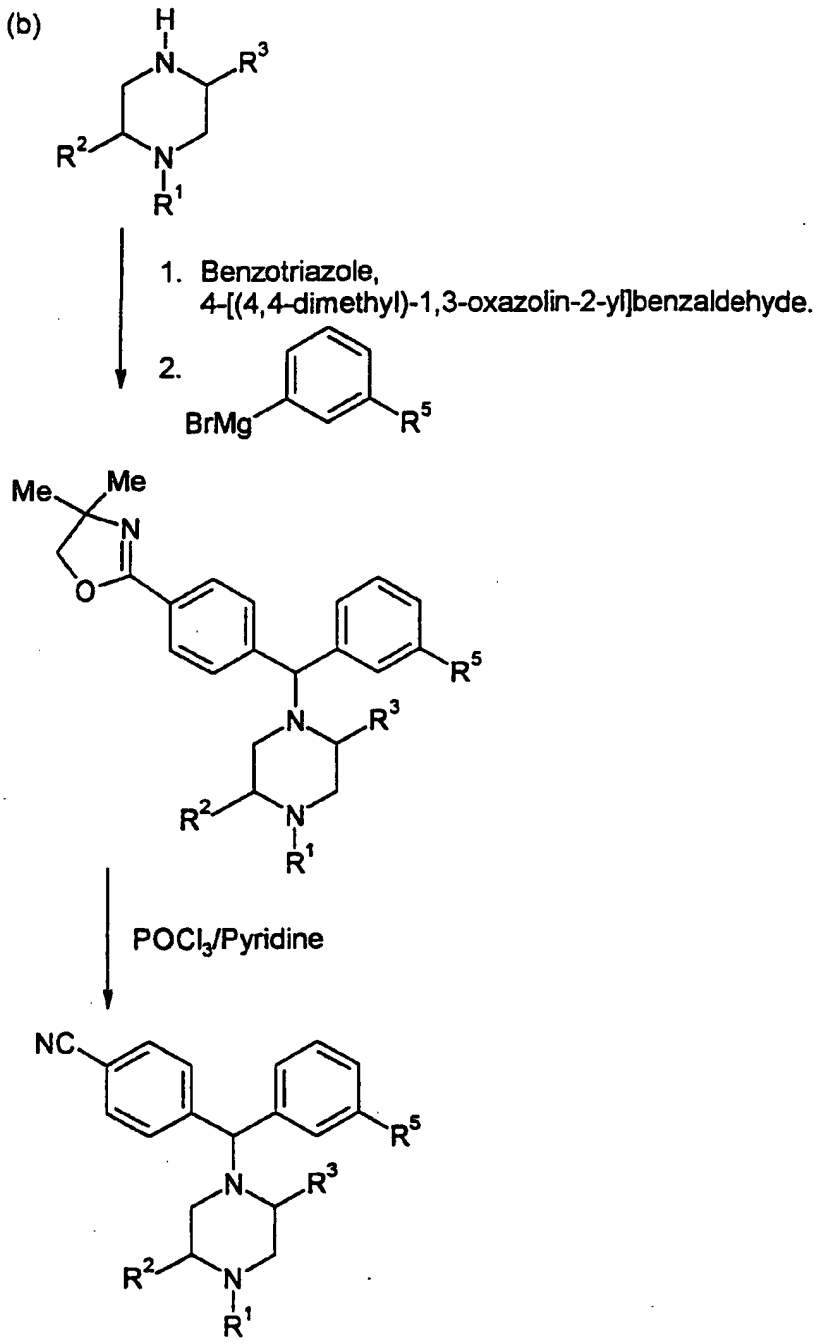
The invention also includes any novel intermediates described herein, particularly those of the formula (II).

The necessary intermediates for the processes described above can be prepared by conventional methods such as those set out in the following Preparations, e.g. as follows:-



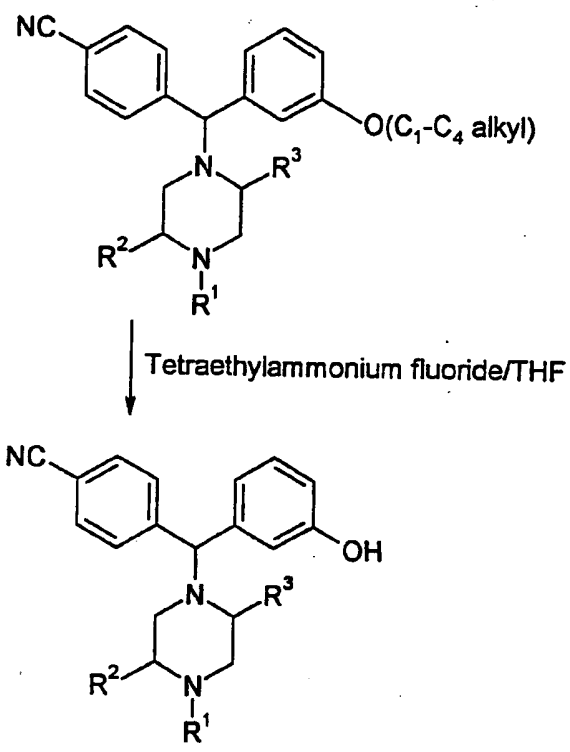
R^1, R^2 and R^3 are as defined for formula (I); TBS = t-butyldimethylsilyl.

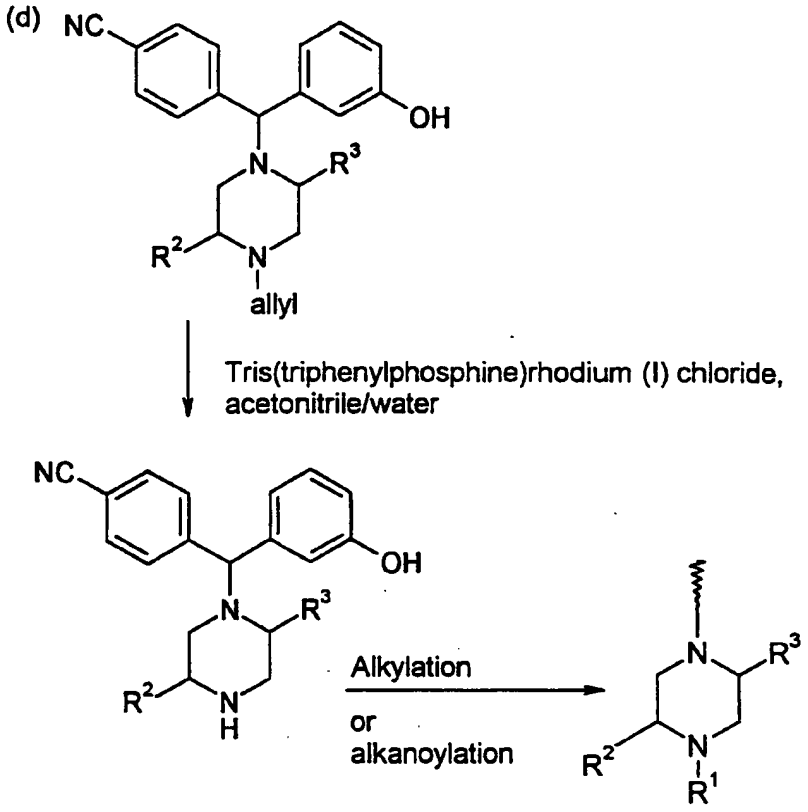
(b)



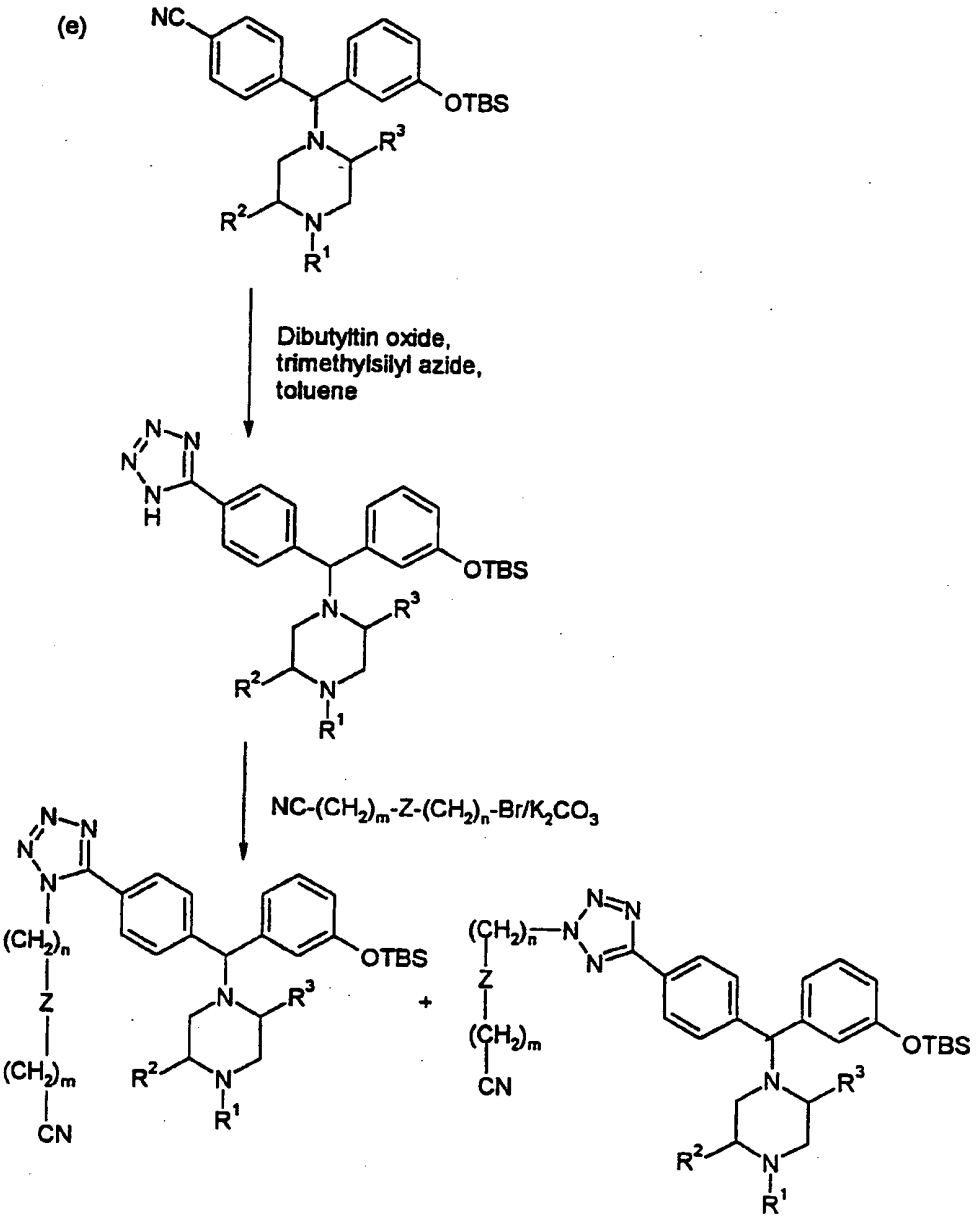
R^1, R^2 and R^3 are as defined for formula (I) and R^5 is C_1-C_4 alkoxy or -$NHSO_2$(C_1-C_4 alkyl).

(c)


NC
O(C1-C4 alkyl)
N
R3
R2
N
R1
Tetraethylammonium fluoride/THF
NC
OH
N
R3
R2
N
R1


(d)
NC
OH
N
R3
R2
N
allyl
Tris(triphenylphosphine)rhodium (I) chloride,
acetonitrile/water
NC
OH
N
R3
R2
N
H
Alkylation
or
alkanoylation
N
R3
R2
N
R1

(e)


NC
OTBS
R3
R2
N
R1
Dibutyltin oxide,
trimethylsilyl azide,
toluene
N
N
N
H
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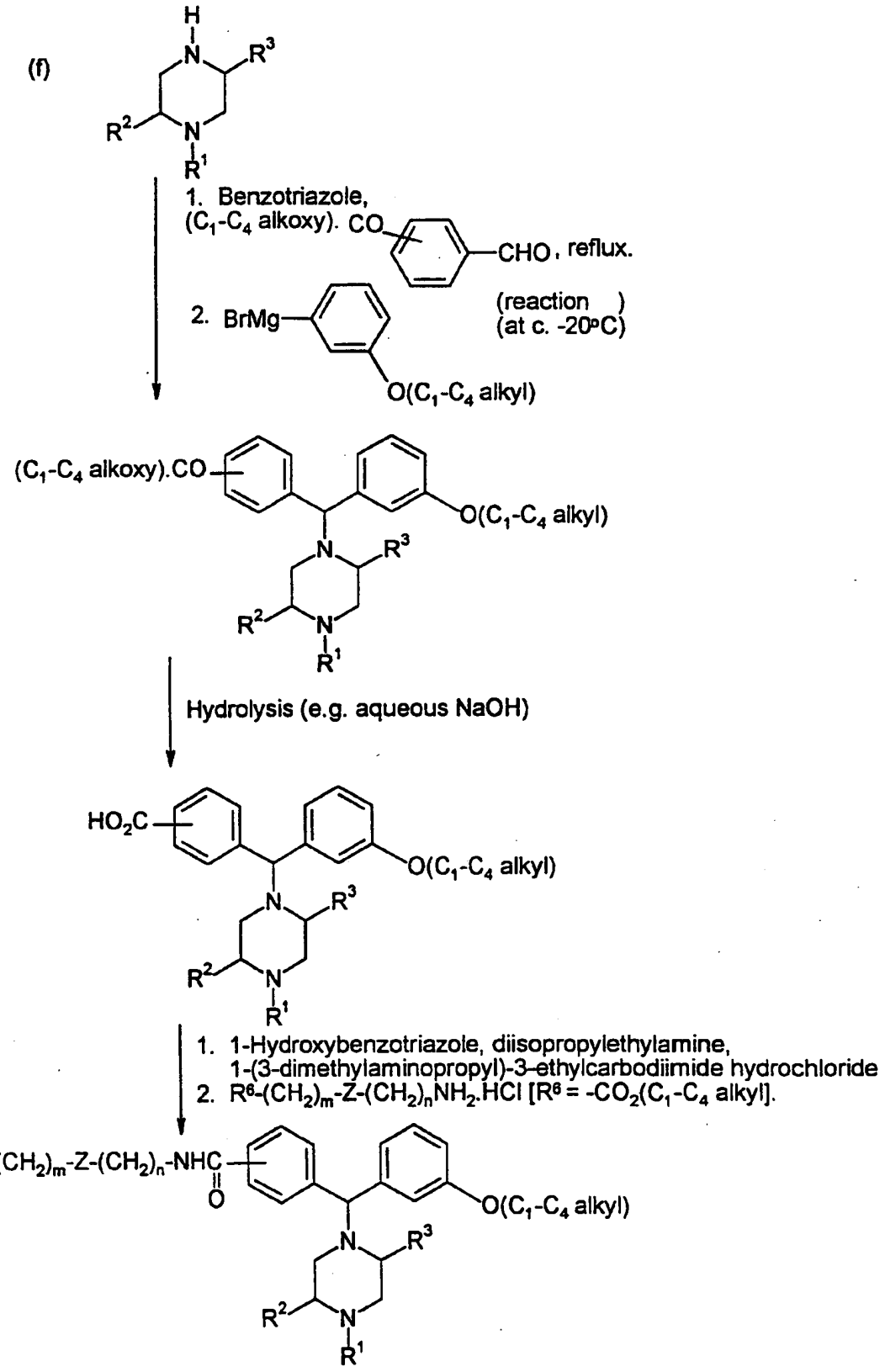
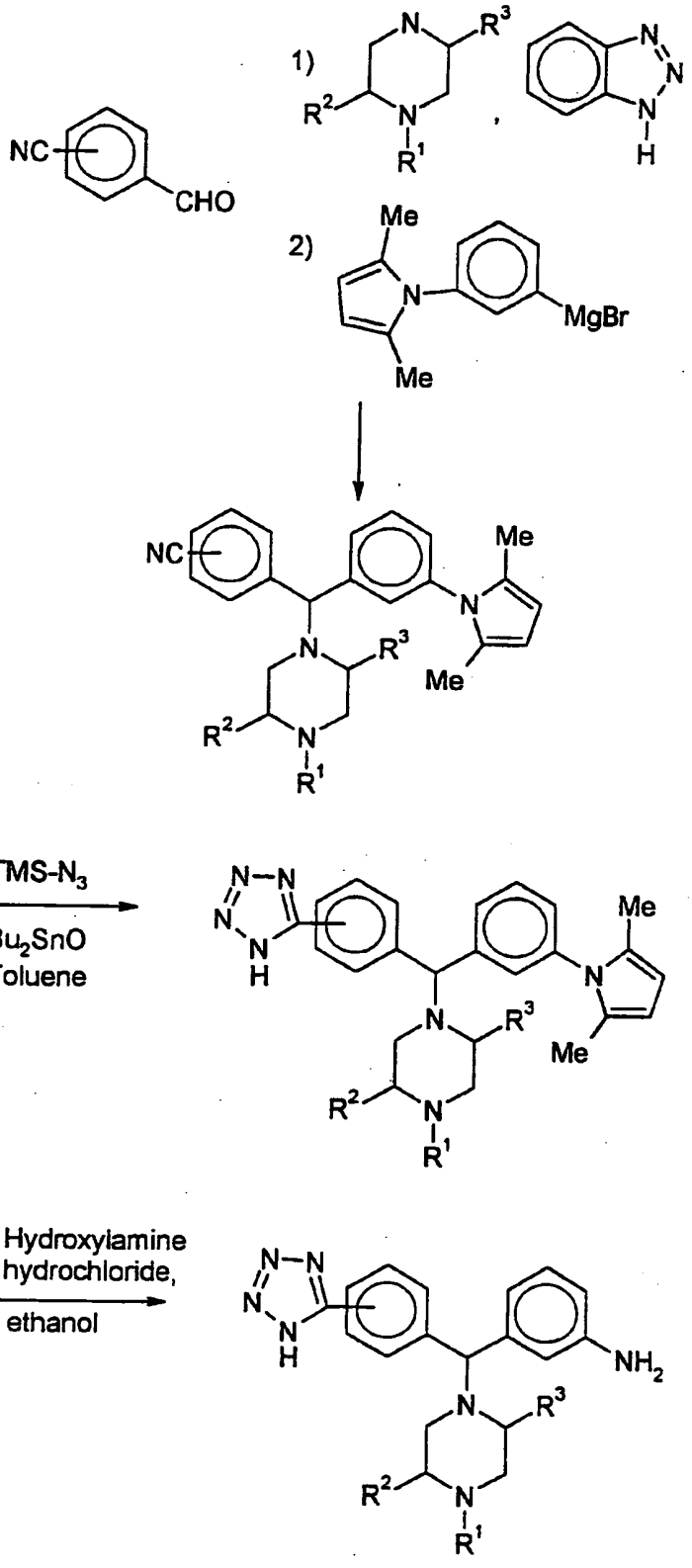
(CH2)n
Z
(CH2)m
CN
+


(f)
1. Benzotriazole,
(C1-C4 alkoxy). CO
CHO, reflux.
2. BrMg
O(C1-C4 alkyl)
(reaction)
(at c. -20°C)
(C1-C4 alkoxy).CO
O(C1-C4 alkyl)
Hydrolysis (e.g. aqueous NaOH)
HO2C
O(C1-C4 alkyl)
1. 1-Hydroxybenzotriazole, diisopropylethylamine,
1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
2. R6-(CH2)m-Z-(CH2)nNH2.HCl [R6 = -CO2(C1-C4 alkyl].
R6-(CH2)m-Z-(CH2)n-NHC
O
O(C1-C4 alkyl)

(g)


1)
2)
MgBr
TMS-N3
Bu2SnO
Toluene
Hydroxylamine
hydrochloride,
ethanol
NH2

Suitable pharmaceutically acceptable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, benzoate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

Suitable pharmaceutically acceptable base salts are formed from bases which form non-toxic salts and examples are the calcium, lithium, magnesium, potassium, sodium, zinc, ethanolamine, diethanolamine and triethanolamine salts.

For a review on suitable salts see Berge et al, J.Pharm.Sci.,66, 1-19 (1977).

As will already be apparent the compounds of the formula (I) will contain one or more asymmetric carbon atoms and will therefore exist in two or more stereoisomeric forms, or they may exist as tautomers. The present invention includes the individual stereoisomers and tautomers of the compounds of the formula (I) and mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound of the formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of the formula (I) may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base.

Receptor binding assays

Opioid (mu and kappa) receptor binding assays were performed in guinea-pig brain membrane preparations. Binding assays were carried out at 25°C for 60 minutes in 50 mM Tris (pH 7.4) buffer. [^{3}H]-DAMGO (2 nM) and [^{3}H]-U-69,593 (2 nM) were used to label mu and kappa receptor binding sites respectively. The protein concentration was approximately 200 µg/well. Non-specific binding was defined with 10 µM naloxone.

Delta receptor binding assay was performed in a stable line of CHO cells expressing the human delta receptor. The binding assay was carried out at 25°C for 120 minutes in 50 mM Tris (pH 7.4) buffer. [^{3}H]-SNC-80 was used to label delta

receptor binding sites. The protein concentration was approximately 12.5 µg/well. Non-specific binding was defined with 10 µM naltrexone.

The binding reaction was terminated by rapid filtration through glass fibre filters, and the samples washed with ice-cold 50 mM Tris buffer (pH 7.4). All assays were performed in duplicate/triplicate.

Isolated tissue studies

Opioid (delta, mu and kappa) activity was studied in two isolated tissues, the mouse vas deferens (MVD)(δ) and the guinea-pig myentric plexus with attached longitudinal muscle (GPMP)(µ and κ).

MVD (DC1 strain, Charles River, 25-35 g) were suspended in 15 ml organ baths containing Mg^{++}-free Krebs' buffer of the following composition (mM): NaCl, 119; KCl, 4.7; $NaHCO_3$, 25; KH_2PO_4, 1.2; $CaCl_2$, 2,5 and glucose, 11. The buffer was gassed with 95% O_2 and 5% CO_2. The tissues were suspended between platinum electrodes, attached to an isometric transducer with 500 mg tension and stimulated with 0.03 Hz pulses of 1-msec pulse-width at supramaximal voltage. IC_{50} values were determined by the regression analysis of concentration-response curves for inhibition of electrically-induced contractions in the presence of 300nM of the mu-selective antagonist CTOP. This test is a measure of δ agonism.

Guinea-pig (Porcellus strain, male, 450-500 g, Dunkin Hartley) myentric plexus with attached longitudinal muscle segments were suspended with 1 g of tension in Krebs' buffer and stimulated with 0.1 Hz pulses of 1-msec pulse-width at supramaximal voltage. Mu functional activity was determined in the presence of 10 nM nor-BNI with 1 µM of the mu selective agonist, DAMGO, added to the bath at the end of the experiment to define a maximal response. This test is a measure of mu functional agonism.

Kappa functional activity was determined in the presence of and 1µM CTOP with 1 µM of the kappa selective agonist U-69,593 added at the end of the experiment to define a maximal response. All inhibitions of twitch height for test compounds were expressed as a percentage of the inhibition obtained with the standard agonist and the corresponding IC_{50} value determined.

DAMGO is [D-Ala2,N-MePhe4,Gly5-ol]enkephalin)

U69593 is ((5a,7a,8b)-(+)-N-methyl-N-(7-[1-pyrrolidinyl]-1-oxaspiro[4,5]dec-8-yl)-benzeneacetamide)

SNC-80 is (+)-4-[(αR)-α((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide
norBNI is nor-binaltorphimine
CTOP is 1,2-Dithia-5,8,11,14,17-pentaazacycloeicosane, cyclic peptide derivative
DPDPE is [D-Pen2,D-Pen5]enkephalin)
[3H]-DAMGO, [3H]-U69593, norBNI, and CTOP are all commercially available from DuPont, Amersham International, RBI and DuPont respectively.
[3H]-SNC80 was prepared by Amersham International.

In general, a therapeutically effective daily oral or intravenous dose of the compounds of formula (I) and their salts is likely to range from 0.01 to 50 mg/kg body weight of the subject to be treated, preferably 0.1 to 20 mg/kg. The compounds of the formula (I) and their salts may also be administered by intravenous infusion, at a dose which is likely to range from 0.001-10 mg/kg/hr.

Tablets or capsules of the compounds may be administered singly or two or more at a time, as appropriate. It is also possible to administer the compounds in sustained release formulations.

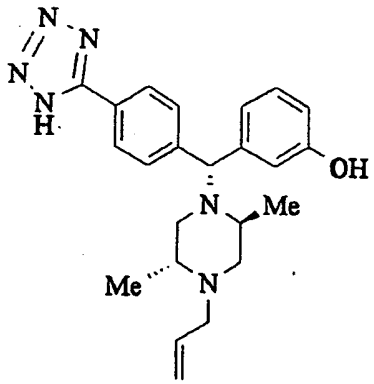
The physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Alternatively, the compounds of the formula (I) can be administered by inhalation or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. An alternative means of transdermal administration is by use of a skin patch. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin. They can also be incorporated, at a concentration of between 1 and 10% by weight, into an ointment consisting of a white wax or white soft paraffin base together with such stabilisers and preservatives as may be required.

The following Examples illustrate the preparation of the compounds (I) and the Preparations illustrate the preparation of novel starting materials.

EXAMPLE 1

(+)-5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole



Boron tribromide (1M solution in dichloromethane; 10ml) was added to a solution of the compound from Example 52 (1g) in dry dichloromethane (20ml) and the resulting solution/suspension was stirred at room temperature for 5 hours. The solvent was evaporated *in vacuo* and the residue basified with methanolic ammonium hydroxide solution and evaporated once again. The residue was purified by column chromatography over silica gel using gradient elution (dichloromethane/methanol/ammonium hydroxide; 93/7/1 to 80/20/3) to afford a foam. This material was further purified over a polystyrene reverse phase resin using gradient elution (100% water/0% acetonitrile to 0% water/100% acetonitrile). The acetonitrile was evaporated *in vacuo* and the remaining aqueous solution was frozen and lyophilised to afford the title compound as a fine white powder, 762mg.

δ_H (300MHz, d_6-DMSO): 9.27 (1H, br s), 7.93 (2H, d), 7.52 (2H, d), 7.13 (1H, t), 6.80-6.60 (3H, m), 5.82 (1H, m), 5.30-5.15 (2H, m), 5.04 (1H, s), 3.37 (1H, dd), 3.10 (1H, dd), 2.92 (1H, m), 2.82 (1H, m), 2.70 (1H, m), 2.66 (1H, m), 2.36 (1H, m), 1.97 (1H, dd), 1.10 (3H, d), 1.02 (3H, d).

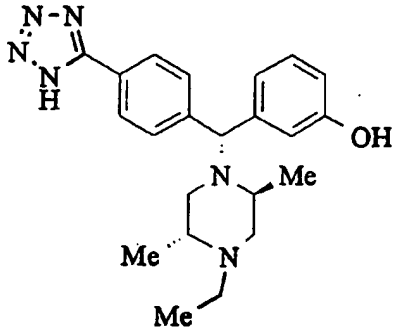
m/z: 405 (MH+)

Found: C, 63.82; H, 7.04; N, 20.09. $C_{23}H_{28}N_6O.0.1NH_4Br$ requires C, 63.90; H, 7.09; 19.76%

$[\alpha]_D$ +13.4° c=0.112, methanol

EXAMPLE 2

(+)-5-{4-[(R)-α-(2(S),5(R)-4-ethyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole



A solution of the compound of Preparation 8 (241mg), dibutyltin oxide (102mg) and trimethylsilyl azide (619mg) in dry toluene (10ml) were heated together under a gentle reflux for 18 hours. The reaction mixture was evaporated to dryness in vacuo and the residue purified by column chromatography over silica gel (80/22/3 dichloromethane/methanol/ammonia) to afford the title compound after trituration with ethyl acetate, 193mg.

m/z: 393 (MH+)

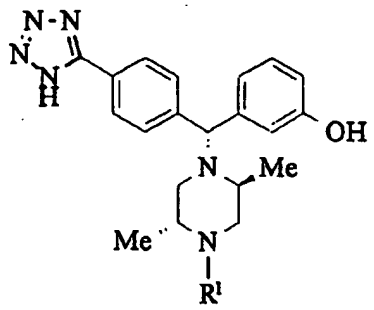
R_f: 0.22 (80/20/3 dichloromethane/methanol/ammonia)

Found: C, 64.99; H, 7.31; N, 19.89. $C_{22}H_{28}N_6O.3/5H_2O.1/6EtOAc$ requires C, 65.12; H, 7.36; N, 20.09%

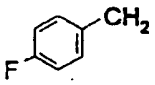
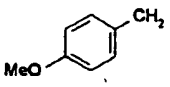
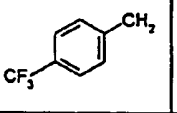
$[\alpha]_D$ +10.8° (c 0.12, methanol)

EXAMPLES 3 to 12

The following compounds of the general formula:



or salts thereof, were prepared from the corresponding nitriles (see Preparations 9 to 13, 16, and 21 to 24) by similar methods to that used in Example 2.

Ex	R^1	*m/z*	R_f (a)	$[\alpha]_D$ (b)	Micro Analysis
3	Pr	407	0.25	+9 c 0.1	Found: C, 65.61; H, 7.69; N, 19.42. $C_{23}H_{30}N_6O.3/5H_2O.1/5EtOAc$ requires C, 65.72; H, 7.60; N, 19.32%
4	Benzyl	455	0.18	-23	Found: C, 68.70; H, 6.73; N, 17.68. $C_{27}H_{30}N_6O.H_2O$ requires C, 68.62; H, 6.83; N, 17.78%
5	Thiazol-2-yl.CH_2-	362	0.30	-34	Found: C, 59.01; H, 6.15; N, 20.11. $C_{24}H_{27}N_7OS.3/2H_2O$ requires C, 59.00; H, 6.19; N, 20.01%
6	Me	379	0.24	+43	Found: C, 63.84; H, 6.99; N, 21.68. $C_{21}H_{26}N_6O.9/10H_2O$ requires C, 63.91; H, 7.10; N, 21.29%
7	$-CH_2CO_2H$	423	0.04	+5	Found: C, 58.86; H, 6.58; N, 20.41. $C_{22}H_{26}N_6O_3.H_2O.1/3NH_3$ requires C, 58.85; H, 6.62; N, 20.28%
8	-COMe	407	0.29	-60	Found: C, 60.77; H, 6.81; N, 21.86. $C_{22}H_{26}N_6O_2.H_2O.4/5NH_4OH$ requires C, 60.78; H, 7.00; N, 21.91%
9	Cyclopropyl.CH_2-	419	0.32	-7	Found: C, 65.79; H, 7.19; N, 19.49. $C_{24}H_{30}N_6O.H_2O$ requires C, 66.03; H, 7.39; N, 19.25%
10		473	0.42	-1° *	Found: C, 66.36; H, 6.24; N, 17.56. $C_{27}H_{29}FN_6O.H_2O$ requires C, 66.59; H, 6.33; N, 17.26%
11		485	0.43	-4° **	Found: C, 66.75; H, 6.70; N, 16.82. $C_{28}H_{32}N_6O_2.H_2O$ requires C, 66.91; H, 6.82; N, 16.72%
12		523	0.44	0° ***	Found: C, 62.29; H, 5.73; N, 16.38. $C_{28}H_{29}F_3N_6O.1/3NH_3.2/3H_2O$ requires C, 62.25; H, 5.85; N, 16.41%

Notes: a) solvent system 80/20/3 dichloromethane/methanol/ammonia; b) c=0.1, methanol; c) $[\alpha]_{365}$ -45° * (c 0.1, methanol); ** d) $[\alpha]_{436}$ -28° (c 0.1, methanol); *** e) $[\alpha]_{365}$ -34°

(c 0.1, methanol);

Example 3. (+)-5-{4-[(R)-α-(2(S),5(R)-4-propyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

Example 4. (-)-5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

Example 5. (-)-5-{4-[(R)-α-(2(S),5(R)-4-thiazol-2-ylmethyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

Example 6. (+)-5-{4-[(R)-α-(2(S),5(R)-4-methyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

Example 7. (+)-5-{4-[(R)-α-(2(S),5(R)-4-carboxymethyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

Example 8. (-)-5-{4-[(R)-α-(2(S),5(R)-4-acetyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

Example 9. (-)-5-{4-[(R)-α-(2(S),5(R)-4-cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

Example 10. (-)-5-{4-[(R)-α-(2(S),5(R)-4-(4-fluorobenzyl)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

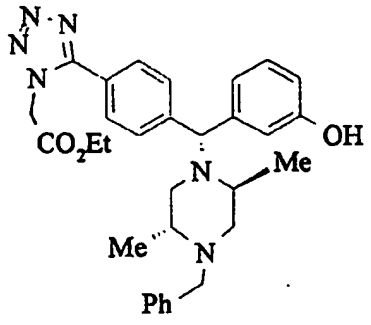
Example 11. (-)-5-{4-[(R)-α-(2(S),5(R)-4-(4-methoxybenzyl)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

Example 12. 5-{4-[(R)-α-(2(S),5(R)-4-(4-trifluromethylbenzyl)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole

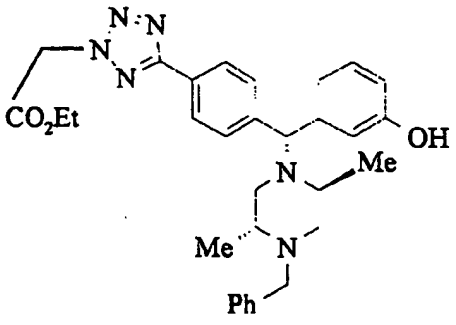
EXAMPLES 13 and 14.

Ethyl (5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)acetate.

Ethyl (5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)acetate.



and



A solution of the compound of Preparation 28 (1.704g), ethyl bromoacetate (501mg)) and potassium carbonate (1.38g) in acetonitrile (40ml)) was heated under a gentle reflux for 2 hours. The cooled reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was separated and extracted with further ethyl acetate. The combined organic extracts were washed with water, saturated brine solution, dried (Na2SO4) and evaporated to dryness in vacuo. The residue was dissolved in tetrahydrofuran (20ml) and tetraethylammonium fluoride (1.11g) in water (2ml) added. The mixture was stirred at room temperature for 18 hours then partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water and saturated brine solution, dried (MgSO4) and evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel (100% hexane to 40% ethyl acetate/hexane) to afford the N-2 isomer, 1.20g, followed by the N-1 isomer, 248mg,.

N-2 Isomer: (Example 13)

m/z: 541 (MH+)

Rf: 0.33 (1/1 hexane/ethyl acetate)

N-1 Isomer: (Example 14)

m/z: 541 (MH+)

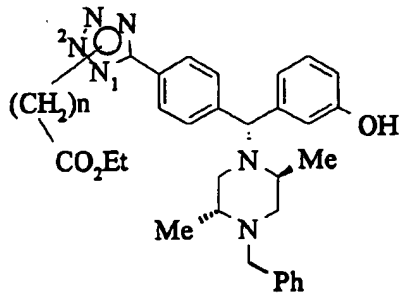
Rf: 0.26 (1/1 hexane/ethyl acetate)

Example 13: δ_H (300Mhz, $CDCl_3$): 7.60 (2H, d), 7.48 (2H, d), 7.34-7.16 (6H, m), 6.80-6.62 (3H, m), 5.18 (2H, s), 5.12 (1H, s), 4.24 (2H, q), 3.92 (1H, d), 3.20 (1H, d), 2.80-2.56 (4H, m), 2.04 (2H, m), 1.24 (3H, q), 1.10 (6H, m)

Example 14 δ_H (300Mhz, $CDCl_3$): 8.18 (2H, d), 7.56 (2H, d), 7.36-7.12 (6H, m), 6.82-6.64 (3H, m), 5.42 (2H, s), 5.20 (1H, br s), 5.10 (1H, s), 4.28 (2H, q), 3.92 (1H, d), 3.20 (1H, d), 2.78-2.56 (4H, m), 2.02 (2H, m), 1.28 (3H, q), 1.10 (6H, m)

EXAMPLES 15 to 18

The following compounds of the general formula:



were prepared by alkylation of the compound of Preparation 28 with a ethyl 4-bromobutyrate or ethyl 5-bromovalerate as appropriate by similar methods to that used in Example 13/14.

Ex	Isomer	n	*m/z*	Rf 1/1 hexane/ethyl acetate
15	N-1	3	569	0.29
16	N-2	3	569	0.42
17	N-1	4	583	0.40
18	N-2	4	583	0.53

Example15. Ethyl 4-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)butyrate.

Example 16. Ethyl 4-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3- hydroxybenzyl]phenyl}-2-tetrazolyl)butyrate

Example 17. Ethyl 5-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3 hydroxybenzyl]phenyl}-1-tetrazolyl)valerate

Example 18. Ethyl 5-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3 hydroxybenzyl]phenyl}-2-tetrazolyl)valerate

Example 15 δ_H (300Mhz, $CDCl_3$): 7.60 (4H, m), 7.36-7.16 (6H, m), 6.80-6.70 (2H, m), 6.62 (1H, m), 5.28 (1H, s), 5.16 (1H, s), 4.52(2H, t), 4.06 (2H, q), 3.96 (1H, d), 3.20 (1H,d), 2.80-2.56 (4H,m), 2.40 (2H,m), 2.24 (2H,m), 2.00 (2H,m), 1.22(3H,t), 1.10 (6H,m).

Example 16 δ_H (300Mhz, $CDCl_3$): 8.02 (2H, d), 7.48 (2H, d), 7.36-7.10 (6H, m), 6.78 (1H,d), 6.70 (1H, d), 6.64 (1H, s), 5.40 (1H, br s), 5.10 (1H, s),

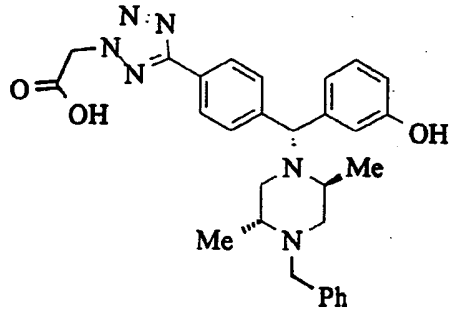
4.72 (2H, m), 4.16 (2H,m), 3.96 (1H, d), 3.20 (1H, d), 2.80-2.56 (4H, m), 2.40 (4H, m), 2.02 (2H, m), 1.24 (3H, t), 1.10 (3H, d), 1.08 (3H, d).

Example 17 δ_H (300Mhz, $CDCl_3$): 8.02 (2H, d), 7.56 (2H, d), 7.36-7.16 (6H, m), 6.80 (1H, d), 6.70 (2H, m), 5.18 (1H, br s), 5.18 (1H, s), 5.10 (1H, s), 4.64 (2H, t), 4.16 (2H, q), 3.92 (1H, d), 3.20 (1H, d), 2.78-2.54 (4H, m), 2.38 (2H, t), 2.18-1.98 (4H, m), 1.72 (2H, m), 1.24 (3H, t), 1.08 (6H, m).

Example 18 δ_H (300Mhz, $CDCl_3$): 7.64 (2H, d), 7.58 (2H, d), 7.36-7.18 (6H, m), 6.78 (2H, m), 6.60 (1H, s), 5.20 (1H, s), 4.42 (2H, t), 4.10 (2H, t), 3.96 (1H, d), 3.20 (1H, d), 2.80-2.56 (4H, m), 2.28 (2H, t), 2.00 (3H, m), 1.60 (4H, m), 1.22 (3H, t), 1.10 (6H, m).

EXAMPLE 19

(+)-5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)acetic acid.



Aqueous sodium hydroxide (2N, 3ml) was added to a solution of the compound of Example 13 (1.15g) in methanol (30ml) and the mixture stirred at room temperature for 18 hours. The reaction was quenched with 2N hydrochloric acid (3ml) and then evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide) to afford the title compound, 977mg.

m/z: 513 (MH+)

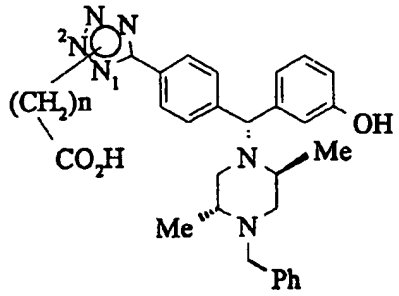
Rf: 0.45 (80/20/3 dichloromethane/methanol/ammonium hydroxide)

$[\alpha]_D$ +6.2° (c 0.1, methanol)

Found: C, 65.37; H, 6.49; N, 16.61. $C_{29}H_{32}N_6O_3.2/3H2O.1/3NH3$ requires C, 65.68; H, 6.53; N, 16.72%

EXAMPLES 20 to 24

The following compounds of the general formula:



or salts thereof, were prepared by hydrolysis of the corresponding esters (see Examples 14 to 18) by similar methods to that used in Example 19.

Ex	Isomer	n	*m/z*	R_f 80/20/3	$[\alpha]_D$	Micro Analysis
20	N-1	1	573	0.48	-16°	Found: C, 65.91; H, 6.41; N, 16.38. $C_{29}H_{32}N_6O_3.3/4H_2O$ requires C, 66.21; H, 6.42; N, 15.97%
21	N-1	3	541	0.33	-9°	Found: C, 67.37; H, 6.73; N, 15.31. $C_{31}H_{36}N_6O_3.1/2H_2O$ requires C, 67.74; H, 6.78; N, 15.29%
22	N-2	3	541	0.32	-13°	Found: C, 67.42; H, 6.79; N, 15.45. $C_{31}H_{36}N_6O_3.1/2H_2O$ requires C, 67.74; H, 6.78; N, 15.29%
23	N-1	4	555	0.12 EtOAc	-23°	Found: C, 67.08; H, 6.99; N, 15.15. $C_{32}H_{38}N_6O_3.2/3H_2O$ requires C, 67.15; H, 7.10; N, 15.49%
24	N-2	4	555	0.21 EtOAc	-0.8°	Found: C, 68.27; H, 6.96; N, 15.09. $C_{32}H_{38}N_6O_3.1/2H_2O$ requires C, 68.18; H, 6.97; N, 14.91%

Example 20 (-)-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)acetic acid.

Example 21 (-)-4-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)butyric acid.

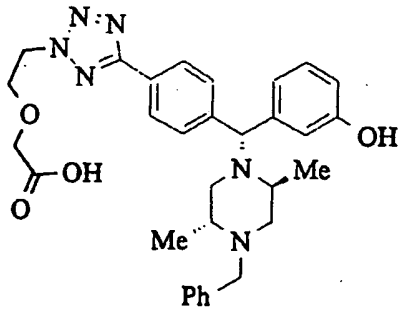
Example 22 (-)-4-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)butyric acid.

Example 23 (-)-5-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid.

Example 24 (-)-5-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valeric acid.

EXAMPLE 25

(+)-(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)ethoxyacetic acid.



A solution of the first compound of Preparation 29 (1.40g) in ethanol (125ml) was cooled to 0°C and saturated with hydrogen chloride gas. After 30 minutes the solvent was evaporated to dryness *in vacuo* to afford a colourless oil. The intermediate imino ether was dissolved in water (50ml), cooled to 0°C and treated with water (50ml). The solution was allowed to warm up to room temperature overnight, after which time aqueous sodium hydroxide solution (5N, 7.5ml) was added and the resulting solution was allowed to stir at room temperature for 1 hour. The reaction mixture was cooled to 0°C, acidified to pH2 and immediately re-basified to pH 9 with 880 ammonium hydroxide. The solvents were evaporated to dryness *in vacuo*, and the residue purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonia) to give the title compound as a gum. The gum was triturated with diethyl ether and filtered to afford the product as a white solid, 1.06g.

m/z: 557 (MH+)

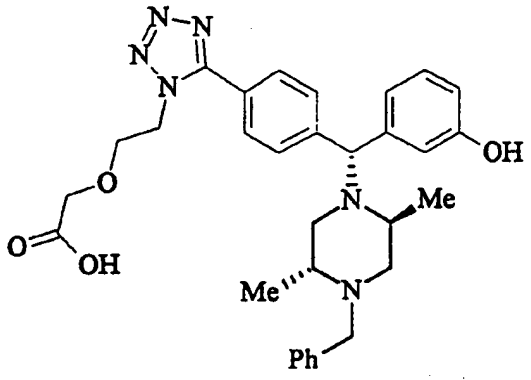
Rf: 0.36 (80/20/3 dichloromethane/methanol/ammonia)

Found: C, 64.73; H, 6.69; N, 15.63. $C_{31}H_{36}N_6O_4.2/3H_2O.1/3NH_3$ requires C, 64.83; H, 6.73; N, 15.44%

$[\alpha]_D$ +2.5° (c 0.12, methanol)

EXAMPLE 26

(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)ethoxyacetic acid.



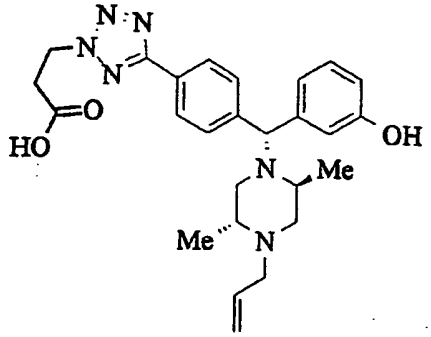
A solution of the second compound of Preparation 29 (137mg) in ethanol (10ml) was saturated with hydrogen chloride gas and stirred at ambient temperature for 1 hour. The solvent was evaporated *in vacuo* to afford a colourless foam which was dissolved in aqueous ethanol (50%, 10ml) and stirred at ambient temperature for 1 hour after which time sodium hydroxide (51mg) was added and stirring continued for 18 hours. The solution was acidified to pH 3.5 with concentrated hydrochloric acid and then basified with ammonium hydroxide solution. The solution was evaporated to dryness *in vacuo*. The residue which was purified by column chromatography over silica gel (dichloromethane/methanol/ammonium hydroxide; 80/20/3) to afford the title compound as a colourless foam, 68mg.

δ_H (400MHz, d_6-DMSO): 7.80 (2H, d), 7.58 (2H, d), 7.28 (4H, m), 7.20 (1H, m), 7.12 (1H, t), 6.72 (1H, m), 6.65 (2H, m), 5.08 (1H, bs s), 4.60 (2H, m), 3.90 (2H, m), 3.80 (1H, m), 3.64 (2H, s), 3.22 (1H, m), 2.70-2.50 (4H, m), 2.00 (1H, m), 1.90 (1H, m), 1.04 (6H, m).

Found: C, 64.36; H, 6.63; N, 15.77. $C_{31}H_{36}N_6O_4.1/2Na.1/2NH_3$ requires C, 64.39; H, 6.49; N, 15.75%

EXAMPLE 27

3-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)propionic acid.



Sodium metal (28.5mg) was added to ethanol (6ml) and allowed to dissolve before the compound from Preparation 31 (643mg) was added and the reaction mixture brought to reflux. After 5 minutes methyl 3-bromopropionate (0.135ml) was added and the reaction mixture was heated with stirring for 18 hours. The solvent was removed by evaporation *in vacuo* and the residue purified by column chromatography over silica gel using gradient elution (99/1/0.25 to 80/20/3; dichloromethane/methanol/ammonium hydroxide) to afford the intermediate, 165mg. The intermediate (165mg) was dissolved in acetonitrile (10ml) and tetraethylammonium fluoride (39.5mg) added. The reaction mixture was stirred for 10 minutes at room temperature and then diluted with water and extracted with ethyl acetate (3X). The combined organic extracts were washed with saturated brine, dried (MgSO4) and evaporated to dryness in vacuo. The residue was purified by column chromatography over silica (97.5/2.5/0.5; dichloromethane/methanol/ammonium hydroxide) to afford an intermediate compound as a 1:1 mixture of methyl and ethyl esters, 72mg.

To a solution of the above intermediate (72mg) in methanol (1.8ml) was added methanolic potassium hydroxide solution (3M, 58μl) and water (0.9ml). The reaction mixture was stirred at room temperature for 18 hours and then quenched with dilute hydochloric acid to pH 5.5. The mixture was evaporated to dryness in vacuo and the residue purified by column chromatography, firstly, over silica gel (85/15/3; dichloromethane/methanol/ammonium hydroxide) and secondly over reverse phase resin using gradient elution (100/0 to 45/55; water/acetonitrile) to afford the title compound after freeze-drying, 40mg.

m/z: 477 (MH+)

Found: C, 62.75; H, 6.93; N, 16.89. $C_{26}H_{32}N_6O3.6/5H_2O$ requires C, 62.78; H, 6.96; N, 16.87%

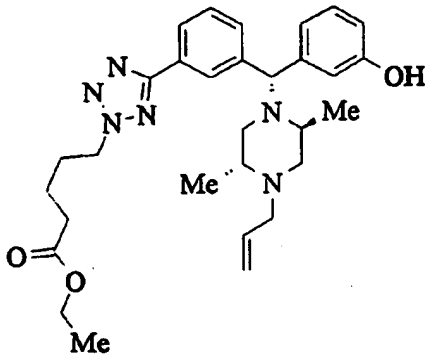
Example 27 δ_H (400Mhz, d_6-DMSO): 9.30 (1H, br s), 7.90 (2H, d), 7.50 (2H, d), 7.06 (1H, t), 6.64 (3H, m), 5.75 (1H, m), 5.10 (1H, d), 5.06 (1H, d), 4.96 (1H, s), 4.80 (2H, t), 3.10 (2H, m), 2.94 (2H, t), 2.80 (1H, dd), 2.68 (1H, d), 2.50 (3H, m), 2.06 (1H, m), 1.82 (1H, t), 1.06 (3H, d), 0.90 (3H, d).

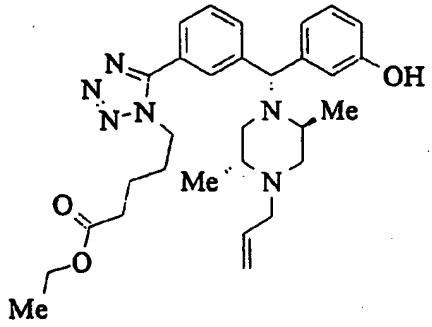
EXAMPLES 28 and 29

Ethyl 5-(5-{3-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valerate.

and

Ethyl 5-(5-{3-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valerate.





A mixture of the compound of Preparation 33 (2.3g), potassium carbonate (1.8g) and ethyl 5-bromovalerate (928mg) in acetonitrile (60ml) was heated under a gentle reflux for 18 hours. The cooled reaction mixture was poured into water, extracted into ethyl acetate, dried (sodium sulphate) and evaporated to dryness *in vacuo*. The crude intermediate was dissolved in acetonitrile (15ml) and tetraethylammonium fluoride (328mg) added. After 20 minutes stirring at room temperature the reaction mixture was poured into water and extracted with ethyl acetate. The combined extracts were washed with water and brine and dried (sodium sulphate), and evaporated to dryness *in vacuo*.

The residue was purified by column chromatography over silica gel (99/1/0.5; diethyl ether/ethanol/ammonium hydroxide) to afford the N-2 isomer, 1550mg

m/z: 533 (MH^+)

R_f: 0.53 (97/3/1; diethyl ether/ethanol/ammonium hydroxide)

and the N-1 isomer, 225mg.

m/z: 533 (MH^+)

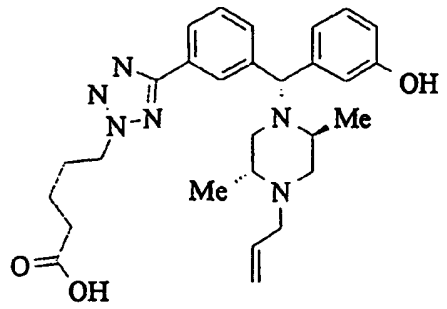
R_f: 0.39 (97/3/1; diethyl ether/ethanol/ammonium hydroxide)

Example 28 δ_H (400Mhz, $CDCl_3$): 8.16 (1H, s), 7.93 (1H, d), 7.53 (1H, d), 7.36 (1H, t), 7.12 (1H, t), 6.73 (1H, d), 6.63 (2H, m), 5.83 (1H, m), 5.72 (1H, br s), 5.20-5.06 (3H, m), 4.63 (2H, t), 4.10 (2H, q), 3.33 (1H, dd), 2.85 (1H, dd), 2.80 (1H, dd), 2.68 (1H, m), 2.60 (1H, d), 2.56 (1H, m), 2.33 (2H, t), 2.16 (1H, dd), 2.06 (2H, m), 1.96 (1H, m), 1.70 (2H, m), 1.20 (3H, t), 1.15 (3H, d), 0.98 (3H, d).

Example 29 δ_H (400Mhz, $CDCl_3$): 7.76 (1H, d), 7.58 (2H, m), 7.50 (1H, t), 7.18 (1H, t), 6.73 (2H, m), 6.63 (1H, s), 6.38 (1H, br s), 5.86 (1H, m), 5.30-5.13 (3H, m), 4.33 (2H, t), 4.13 (2H, q), 3.36 (1H, dd), 2.86 (2H, m), 2.70 (1H, m), 2.60 (1H, m), 2.50 (1H, m), 2.28 (2H, t), 2.16 (1H, dd), 1.98 (1H, dd), 1.90 (2H, m), 1.58 (2H, m), 1.26 (3H, t), 1.18 (3H, d), 1.00 (3H, d).

EXAMPLE 30

(+)-5-(5-{3-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valeric acid.



Aqueous sodium hydroxide (2N, 2ml) was added to a solution of the compound of Example 28 (1.15g) in dioxane (4ml) and methanol (2ml) and the mixture stirred at room

temperature for 90 minutes. The reaction was quenched with 2N hydrochloric acid (3ml) and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography over polystyrene resin using gradient elution (water/acetonitrile; 100/0 to 40/60) to afford the title compound after freeze-drying, 690mg.

R_f: 0.20 (80/20/3; dichloromethane/methanol/ammonium hydroxide)

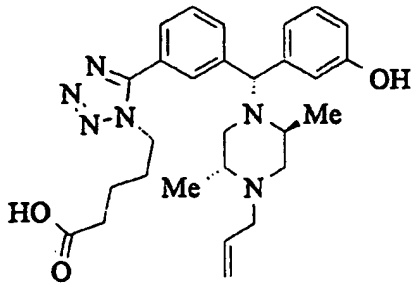
m/z: 505 (MH^+)

$[\alpha]_D$ +13.6 (c=0.11, methanol)

Found: C, 64.83; H, 7.10; N, 16.21. $C_{28}H_{36}N_6O_3.7/10H_2O$ requires C, 65.02; H, 7.29; N, 16.25%

EXAMPLE 31

(+)-5-(5-{3-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid.



Aqueous sodium hydroxide (2N, 1ml) was added to a solution of the compound of Example 29 (225mg) in dioxane (2ml) and methanol (1ml) and the mixture stirred at room temperature for 18 hours. The reaction was quenched with 2N hydrochloric acid (3ml) and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography over polystyrene resin using gradient elution (water/acetonitrile; 100/0 to 0/100) to afford the title compound after freeze-drying, 169mg.

R_f: 0.21 (80/20/3; dichloromethane/methanol/ammonium hydroxide)

m/z: 505 (MH^+)

$[\alpha]_D$ +13.54 (c=0.11, methanol)

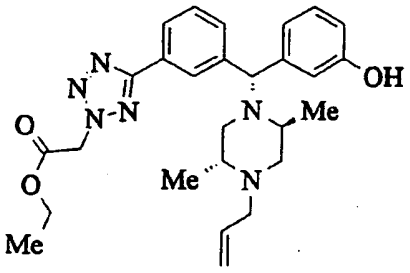
Example 31 δ_H (400Mhz, d_6-DMSO): 11.2 (1H, br s), 7.76-7.48 (4H, m), 7.06 (1H, t), 6.70 (2H, m), 6.60 (1H, d), 5.76 (1H, m), 5.20-5.00 (3H, m), 4.40 (2H, m), 3.30 (1H, br s), 3.16 (1H, m), 2.90-2.40 (5H, m), 2.16-1.98 (3H, m), 1.90-1.68 (3H, m), 1.38 (2H, m), 1.06 (3H, d), 0.92 (3H, d).

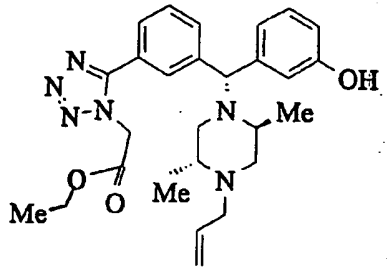
EXAMPLES 32 and 33

Ethyl (5-{3-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)acetate.

and

Ethyl (5-{3-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)acetate.





A mixture of the compound of Preparation 33 (2.3g), potassium carbonate (1.8g) and ethyl bromoacetate (702mg) in acetonitrile (60ml) was heated under a gentle reflux for 3 hours. The cooled reaction mixture was poured into water, extracted into ethyl acetate, dried (sodium sulphate) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (90/10/0.75; hexane/isopropanol/ammonium hydroxide) to afford two products with the order of elution N-2 isomer, 1200mg

m/z: 491 (MH+)

R_f: 0.21 (95/5; dichloromethane/methanol)

and the N-1 isomer, 140mg

m/z: 491 (MH+)

R_f: 0.23 (95/5; dichloromethane/methanol)

Example 32 δ_H (300Mhz, d_6-DMSO): 9.30 (1H, s), 8.10 (1H, s), 7.86 (1H, d), 7.58 (1H, d), 7.50 (1H, t), 7.14 (1H, t), 6.74-6.64 (3H, m), 5.86 (2H, s), 5.76 (1H, m), 5.20-5.00 (3H, m), 4.20 (2H, q), 3.16 (1H, m), 2.85 (1H, dd), 2.73 (1H, d), 2.56 (3H, m), 2.10 (1H, dd), 1.90 (1H, dd), 1.20 (3H, t), 1.06 (3H, d), 0.96 (3H, d).

Example 33 δ_H (300Mhz, $CDCl_3$): 7.70 (2H, m), 7.56 (1H, d), 7.48 (1H, t), 7.18 (1H, t), 6.74 (2H, d), 6.60 (1H, s), 5.86 (1H, m), 5.70 (1H, br s), 5.30-5.10 (5H, m), 4.18 (2H, q), 3.38 (1H, dd), 2.86 (2H, m), 2.66 (1H, m), 2.54 (2H, m), 2.16 (1H, t), 1.94 (1H, t), 1.18 (6H, m), 1.00 (3H, d).

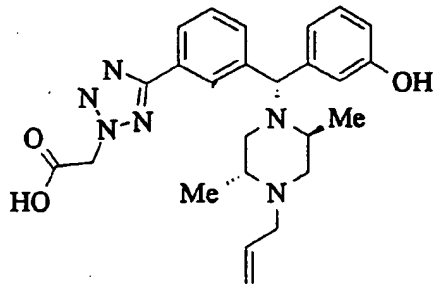
EXAMPLES 34 and 35

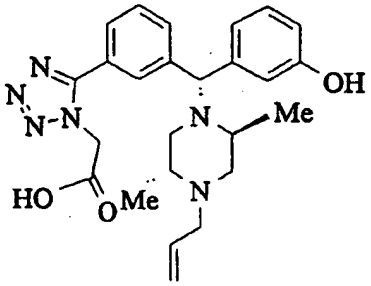
(+)-(5-{3-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)acetic acid.

and

(5-{3-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)acetic acid.

The following compounds of the formula:





were prepared from the corresponding esters (see Examples 32 and 33) by similar methods to Example 31

N-2 isomer: (Example 34)

m/z: 463 (MH+)

R_f: 0.22 (80/20/3; dichloromethane/methanol/ammonium hydroxide)

Found: C, 62.71; H, 6.65; N, 17.66. $C_{25}H_{30}N_6O_3.9/10H_2O$ requires C, 62.72; H, 6.69; N, 17.55%

$[\alpha]_D$ +19.8° (c=0.113, methanol)

N-1 isomer: (Example 35)

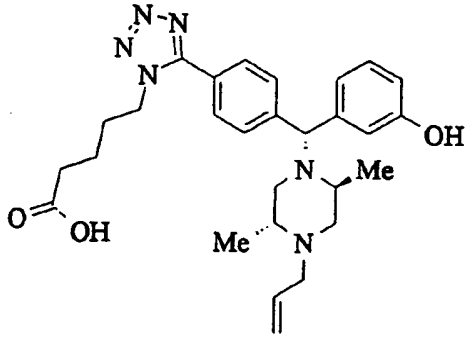
m/z: 463 (MH+)

R_f: 0.27 (80/20/3; dichloromethane/methanol/ammonium hydroxide)

Found: C, 60.86; H,6.60; N, 17.02. $C_{25}H_{30}N_6O_3.8/5H_2O$ requires C, 61.11; H, 6.81; N, 17.10%

EXAMPLE 36

(+)-5-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid



To a solution of the compound of Example 53 (2.42g) in dichloromethane (50ml) was added boron tribromide (18ml of 1M solution in dichloromethane), and the resulting solution was stirred at room temperature for 3 hours. The mixture was evaporated to dryness in vacuo and the residue was basified with ethanolic ammonia and re-evaporated to dryness. A solution of the residue in ethanol (120ml) and dioxane (20ml) was added aqueous sodium hydroxide solution (2N, 26ml) was stirred at room temperature for 18 hours. The solution was acidified to pH 3 with hydrochloric acid, and then immediately re-basified to pH 9 with 880 ammonia solution, and evaporate to dryness in vacuo. The residue was purified by column chromatography over silica gel (80/20/3; dichloromethane/methanol/ammonia) to afford the title compound which was further purified by chromatography over polystyrene resin (gradient elution; 100% water to 40% acetonitrile/water). The aqueous solution of the product was freeze dried to afford the title compound as a floculent white solid, 0.545g.

m/z: 505 (MH+)

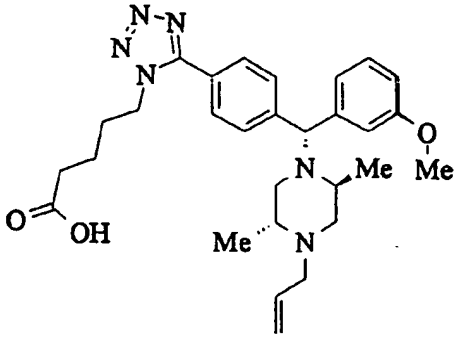
Rf: 0.22 (80/20/3; dichloromethane/methanol/ammonia)

Found: C, 64.48; H, 7.25; N, 16.14. $C_{28}H_{36}N_6O_3.H_2O$ requires C, 64.35; H, 7.33; N, 16.08%

$[\alpha]_D$ +21.8°

EXAMPLE 37

5-{5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]phenyl}-1-tetrazolyl}valeric acid.



To a solution of the compound of Example 53 (350mg) in dioxane (20ml) and methanol (6ml) was added 1N aqueous sodium hydroxide solution (3.2ml). The reaction mixture was stirred at ambient temperature for 3 hours, acidified to pH 2 with hydrochloric acid and immediately basified to pH 9 with 880 ammonia. Rotary evaporation followed by purification of the residue by column chromatography over reverse phase polystyrene resin using gradient elution (100% water to 100% acetonitrile) afforded the title compound as a colourless solid, 272mg.

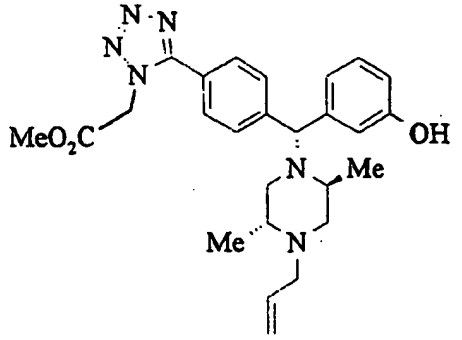
m/z: 519 (MH^+)

R_f: 0.33 (80/20/3 dichloromethane/methanol/ammonia)

Example 37 δ_H (300Mhz, $CDCl_3$): 7.59 (4H, m), 7.22 (1H, m), 6.90 (2H, m), 6.69 (1H, m), 5.87 (2H, m), 5.22 (3H, m), 4.48 (2H, t), 3.78 (3H, s), 3.40 (1H, m), 2.89 (1H, m), 2.70 (3H, m), 2.20 (4H, m), 1.83 (2H, m), 1.58 (2H, m), 1.08 (6H, m).

EXAMPLE 38

Methyl (5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)acetate



Diethyl azidodicarboxylate (1.46g) was added to an ice-cold solution of the compound of Preparation 40 (3.96g), triphenylphosphine (2.26g) and trimethylsilyl azide (1.16g) in dry toluene (15ml). The reaction was stirred at 0°C for 1 hour, room temperature for 18 hours, and 50°C for 5 days. The solvent was evaporated in vacuo and the residue purified by column chromatography over silica gel using gradient elution (dichloromethane to 95/5 dichloromethane/methanol) to afford the title compound, 520mg.

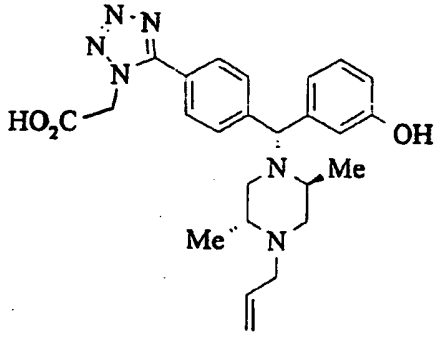
m/z: 477 (MH+)

Rf: 0.25 (95/5/0.5 dichloromethane/methanol/ammonia)

Example 38 δ_H (300Mhz, d_6-DMSO): 9.30 (1H, br s), 7.72 (2H, d), 7.57 (2H, d), 7.17 (1H, t), 6.72 (2H, m), 6.63 (1H, m), 5.90 (1H, m), 5.38-5.18 (5H, m), 3.82 (3H, s), 3.60 (1H, br s), 3.43 (1H, m), 2.90 (2H, m), 2.68 (1H, m), 2.57 (2H, m), 2.18 (1H, m), 1.98 (1H, m), 1.20 (3H, d), 1.03 (3H, d).

EXAMPLE 39

(+)-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)acetic acid.



To a solution of the compound of Example 38 (515mg) in dioxane (8ml) and methanol (20ml) was added 5N aqueous sodium hydroxide solution (2.16ml). The reaction mixture was stirred at ambient temperature for 18 hours, acidified to pH 2 with hydrochloric acid and immediately basified to pH 10 with 880 ammonia. Rotary evaporation followed by purification of the residue by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonia) and over reverse phase polystyrene resin using gradient elution (100% water/0% acetonitrile to 100% acetonitrile/0% water) afforded the title compound as a solid, 373mg.

m/z: 463 (MH+)

Rf: 0.23 (80/20/3 dichloromethane/methanol/ammonia)

$[\alpha]_D$ +17.6° (c 0.125, methanol)

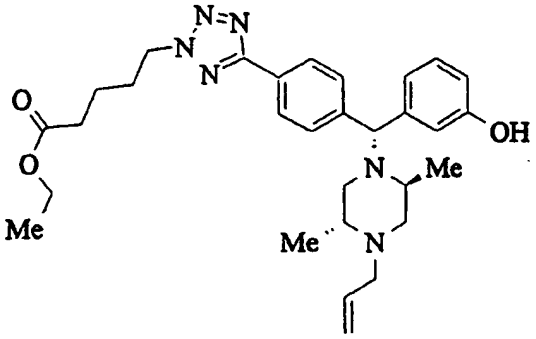
Found: C, 62.94; H, 6.67; N, 17.90. $C_{25}H_{30}N_6O_3.4/5H_2O$ requires C,62.96; H, 6.68; N, 17.62%

EXAMPLES 40 and 41

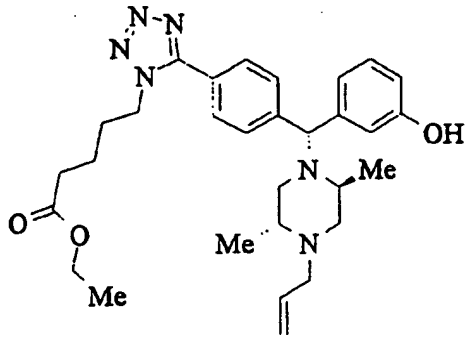
(+)-5-Ethyl (5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valerate.

and

Ethyl 5-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valerate.



and



A mixture of the compound of Preparation 31 (2g), potassium carbonate (1.60g) and ethyl 5-bromovalerate (807mg) in acetonitrile (20ml) was heated under a gentle reflux for 18 hours. The cooled reaction mixture was poured into water, extracted into ethyl acetate, dried (sodium sulphate) and evaporated to dryness *in vacuo*. The crude intermediate was dissolved in acetonitrile (20ml) and tetraethylammonium fluoride

(865mg) added. After 20 minutes stirring at room temperature the reaction mixture was poured into water and extracted with ethyl acetate. The combined extracts were washed with water and brine and dried (sodium sulphate), and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (90/10/0.75; hexane/isopropanol/ammonium hydroxide) to afford the N-2 isomer, 1.60g.

m/z: 533 (MH+)

Rf: 0.30 (85/15/1; hexane/isopropanol/ammonium hydroxide)

and the N-1 isomer, 150mg.

m/z: 533 (MH+)

Rf: 0.48 (93/7/1; dichloromethane/methanol/ammonium hydroxide)

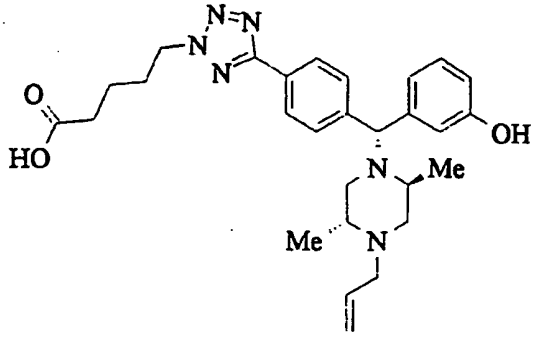
Example 40 $[\alpha]_D = +18.7°$ (c=0.11, methanol)

Found: C, 67.34; H, 7.71; N, 15.39. $C_{30}H_{40}N_6O_3$ requires C, 67.64; 7.57; N, 15.78%

Example 41 δ_H (300Mhz, $CDCl_3$): 7.64 (2H, d), 7.58 (2H, d), 7.18 (1H, t), 6.70 (2H, m), 6.62 (1H, s), 5.88 (1H, m), 5.30 (1H, s), 5.22 (1H, d), 4.96 (1H, d), 4.42 (2H,t), 4.10 (2H, q), 3.38 (1H, dd), 2.90 (2H, m), 2.72 (1H, m), 2.56 (2H, m), 2.30 (2H, t), 2.18 (1H, t), 1.98 (3H, m), 1.62 (2H, m), 1.22 (6H, m), 1.02 (3H, d).

EXAMPLE 42

(+)-5-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valeric acid.



A solution of the compound of Preparation 1 (40g), benzotriazole (30.9g) and the compound of Preparation 43 (78.4g) in toluene (780ml) was heated under reflux with azeotropic removal of water for 24 hours. The solution was cooled to -20°C for the dropwise addition of the 3-trimethylsilyloxyphenylmagnesium bromide [704ml of a

solution prepared from 158.7g of the compound of Preparation 44 and magnesium turnings (17.3g) in tetrahydrofuran (800ml] at such a rate as to maintain the internal temperature in the range -20 to -15°C. The resulting solution was stirred at -20°C for 5 minutes and then warmed to room temperature overnight. The reaction was quenched with 10% aqueous ammonium chloride solution (2000ml). The organic phase was washed with water (1000ml), dried ($MgSO_4$) and evaporated to dryness *in vacuo* to afford the ethyl ester of the title compound, 101g as a red oil which was identical to the compound of Example 40

m/z: 533 (MH^+)

R_f: 0.30 (85/15/1; hexane/isopropanol/ammonium hydroxide)

To a solution of the intermediate ester (14g) in tetrahydrofuran (90ml) was added sodium hydroxide solution (86ml of a 2N solution) and the mixture stirred at room temperature for 18 hours. The layers were separated and the aqueous solution cooled in an ice-bath for the addition of 2N hydrochloric acid (86ml) over 20 minutes. The aqueous solution was extracted with ethyl acetate (2X75ml). The combined organic extracts were dried (Na2SO4) and evaporated to dryness *in vacuo*, and the residue purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonia) to afford the title compound, 5.2g.

m/z: 505 (MH+)

R_f: 0.28 (80/20/3 dichloromethane/methanol/ammonia)

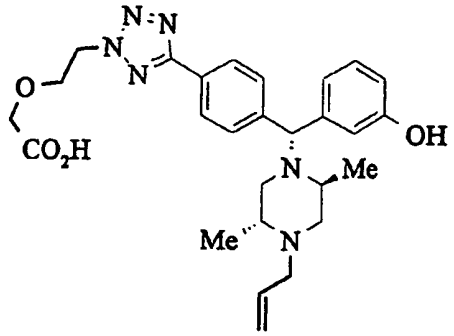
$[\alpha]_D$ +18.5° (c 0.124, methanol)

Found: C, 64.85; H, 7.16; N, 16.28. $C_{28}H_{36}N_6O_3.4/5H_2O$ requires C,64.79; H, 7.30; N, 16.19%

Example 42 δ_H (400Mhz, d_6-DMSO): 9.20 (1H, br s), 7.96 (2H, d), 7.53 (2H, d), 7.12 (1H,t), 6.66 (3H, m), 5.77 (1H, m), 5.18 (1H, m), 5.13 (1H, d), 5.07 (1H, s), 4.69 (2H, t), 3.36 (1H, br s), 3.15 (1H, dd), 2.84 (1H, dd), 2.73 (1H, dd), 2.65-2.47 (3H, m), 2.15 (2H, t), 2.07 (1H, dd), 1.95 (2H, m), 1.86 (1H, m), 1.46 (2H, m),1.07 (3H, d), 0.94 (3H, d).

EXAMPLE 43

(+)-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)ethoxyacetic acid.



A solution of the compound of Preparation 41 (3.46g) in ethanol (200ml) was cooled to 0°C and saturated with hydrogen chloride gas. After 30 minutes the solvent was evaporated to dryness in vacuo to afford a colourless oil. The intermediate imino ether was dissolved in water (50ml), cooled to 0°C and treated with water (50ml). The solution was allowed to warm up to room temperature overnight, after which time aqueous sodium hydroxide solution (5N, 7.5ml) was added and the resulting solution was allowed to stir at room temperature for 1 hour. The reaction mixture was cooled to 0°C, acidified to pH2 and immediately re-basified to pH 9 with 880 ammonium hydroxide. The solvents were evaporated to dryness in vacuo, and the residue purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonia) to give the title compound as a gum. The gum was dissolved in water and freeze-dried to afford the desired product as a white solid, 3.30g.

m/z: 506 (MH+)

M.pt.: 137-140°

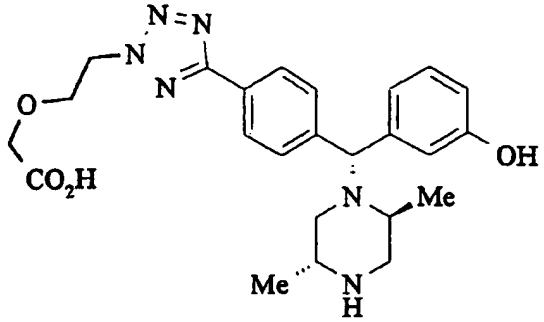
Rf: 0.18 (80/20/3 dichloromethane/methanol/ammonia)

Found: C, 62.15; H, 6.83; N, 16.23. $C_{27}H_{34}N_6O_4.4/5H_2O$ requires C, 62.24; H, 6.89; N, 16.13%

$[\alpha]_D$ +17.3° (c 0.11, methanol)

EXAMPLE 44

(5-{4-[(R)-α-(2(S),5(R)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)ethoxyacetic acid.



Tris(triphenylphosphine)rhodium(I) chloride (100mg) was added to a solution of the compound of Example 43 (620mg) in acetonitrile (20ml) and water (5ml). The reaction mixture was heated under a gentle reflux and the solvent allowed to distil off slowly. Additional acetonitrile/water (100ml; 4:1 v/v) was added a such a rate as to maintain a steady distillation. After the addition of solvent was complete the distillation was continued until the volume was reduced to approximately 50ml. The cooled solution was poured into ethyl acetate and washed with saturated aqueous sodium bicarbonate solution and brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide;) to afford the title compound, 123mg together with unreacted starting material, 460mg.

m/z: 467 (MH+)

Rf: 0.06 (80/20/3 dichloromethane/methanol/ammonia)

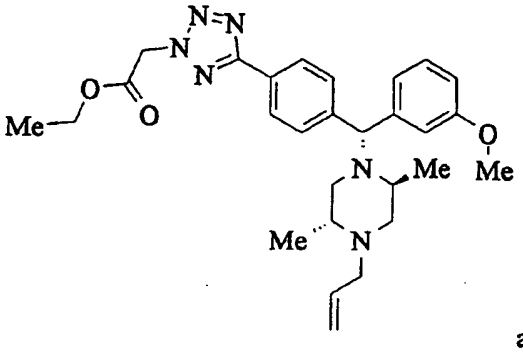
Example 44 δ_H (400Mhz, d_6-DMSO): 8.00 (2H, d), 7.52 (2H, d), 7.18 (1H, t), 6.80-6.60 (3H, m), 4.86 (2H, m), 4.02 (2H, m), 3.80 (2H, s), 3.50-3.00 (6H, br m), 2.66 (2H, m), 1.85 (2H, m), 1.17 (3H, d), 1.02 (3H, d).

EXAMPLE 45 and 46

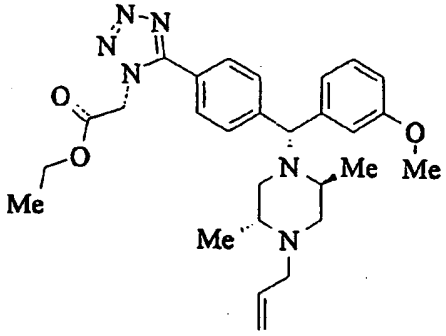
Ethyl (5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]phenyl}-2-tetrazolyl)acetate.

and

Ethyl (5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]phenyl}-1-tetrazolyl)acetate.



and



A mixture of the compound of Example 52 (1.0g), potassium carbonate (990mg) and ethyl bromoacetate (265µl) in dry dichloromethane (30ml) was heated under a gentle reflux for 18 hours. The cooled reaction mixture was poured into water, extracted with dichloromethane, dried (sodium sulphate) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (90/10/0.75; hexane/isopropanol/ammonium hydroxide) to afford the N-2 isomer (Example 45), 620mg followed by the N-1 isomer (Example 46), 518mg.

Example 45:

m/z: 505 (MH+)

Rf: 0.29 (90/10/0.75; hexane/isopropanol/ammonium hydroxide)

Example 46:

m/z: 505 (MH+)

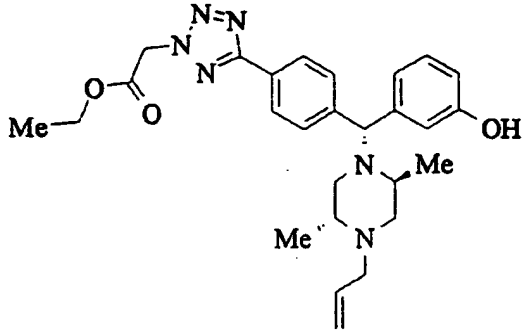
Rf: 0.14 (90/10/0.75; hexane/isopropanol/ammonium hydroxide)

Example 45 δ_H (300Mhz, $CDCl_3$): 8.07 (2H, d), 7.58 (2H, d), 7.23 (1H, m), 6.8 (3H, m), 5.86 (1H, m), 5.43 (2H, s), 5.19 (3H, m), 4.30 (2H, q), 3.79 (3H, s), 3.38 (1H, dd), 2.84 (2H, m), 2.63 (2H, m), 2.51 (1H, m), 2.14 (1H, m), 1.93 (1H, m), 1.30 (3H, t), 1.20 (3H, d), 1.00 (3H, d).

Example 46 δ_H (300Mhz, $CDCl_3$): 7.65 (4H, q), 7.27 (1H, m), 6.3 (3H, m), 5.86 (1H, m), 5.30-5.10 (5H, m), 4.28 (2H, q), 3.80 (3H, s), 3.37 (1H, dd), 2.90-2.40 (5H, m), 2.15 (1H, m), 1.93 (1H, m), 1.27 (3H, t), 1.20 (3H, d), 1.00 (3H, d).

EXAMPLE 47

Ethyl (5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)acetate.



Boron tribromide (1M in dichloromethane, 2.46ml) was added to a solution of the compound of Example 45 (620mg) and stirred at room temperature for 6 hours. The reaction mixture was evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel using gradient elution (95/5/0.5 to 80/20/3 dichloromethane/methanol/ammonium hydroxide) to afford the title compound, 212mg.

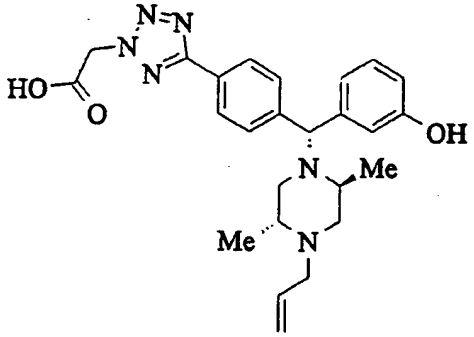
m/z: 491 (MH+)

Rf: 0.50 (93/7/1 dichloromethane/methanol/ammonium hydroxide)

Example 47 δ_H (300Mhz, $CDCl_3$): 8.07 (2H, d), 7.57 (2H, d), 7.17 (1H, t), 6.73 (3H, m), 5.88 (1H, m), 5.40 (2H, m), 5.20-5.10 (3H, m), 4.28 (2H, q), 3.36 (1H, dd), 2.88 (1H, dd), 2.82 (1H, m), 2.78-2.44 (3H, m), 2.17 (1H, dd), 1.98 (1H, dd), 1.50 (1H, br s), 1.30 (3H, t), 1.17 (3H, d), 1.00 (3H, d).

EXAMPLE 48

(+)-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)acetic acid.



To a solution of the compound of Example 47 (168mg) in dioxane (4ml) and methanol (6ml) was added 2N aqueous sodium hydroxide solution (0.86ml). The reaction mixture was stirred at ambient temperature for 18 hours, acidified to pH 2 with 2N hydrochloric acid and immediately basified to pH 10 with 880 ammonia. Rotary evaporation followed by purification of the residue by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonia) and over reverse phase polystyrene resin using gradient elution (100% water/0% acetonitrile to 100% acetonitrile/0% water) afforded the title compound as a solid after freeze-drying, 130mg.

m/z: 462 (MH+)

Rf: 0.21 (80/20/3 dichloromethane/methanol/ammonia)

$[\alpha]_D$ +20° (c 0.12, methanol)

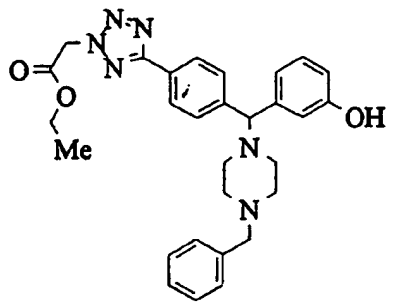
Found: C, 62.17; H, 6.60; N, 17.25. $C_{25}H_{30}N_6O_3.H_2O$ requires C,62.48; H, 6.71; N, 17.49%

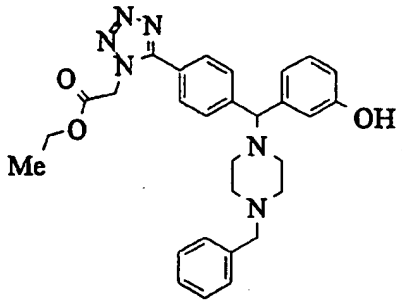
EXAMPLES 49 and 50

(±)-Ethyl 2-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]-phenyl}-2-tetrazolyl)acetate

and

(±)-Ethyl 2-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]-phenyl}-1-tetrazolyl)acetate





A solution of the compound of Preparation 4(b) (0.54g), ethyl bromoacetate (167mg) and cesium carbonate (0.49g) in dimethylformamide (20ml) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between saturated sodium chloride solution and ethyl acetate. The aqueous layer was separated and extracted with further ethyl acetate. The combined organic extracts were washed with water, saturated brine solution, dried (sodium sulphate) and evaporated to dryness *in vacuo*. The residue was dissolved in tetrahydrofuran (20ml) and tetraethylammonium fluoride (400g) in water (2ml) added. The mixture was stirred at room temperature for 12 hours then partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water and saturated brine solution, dried (magnesium sulphate) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (25-50% ethyl acetate/hexane) to afford in order of elution the N-2 isomer, 310mg, followed by the N-1 isomer, 75mg,.

N-2 Isomer: (Example 49):

m/z: 513 (MH^+)

δ_H (300MHz, d_6-DMSO): 9.28 (1H, s), 7.94 (2H, d), 7.56 (2H, d), 7.32-7.14 (5H, m), 7.06 (1H, t), 6.80 (2H, m), 6.56 (1H, d), 5.82 (2H, s), 4.26 (1H, s), 4.20 (2H, q), 3.46 (2H, s), 2.50-2.20 (8H, m), 1.20 (3H, t).

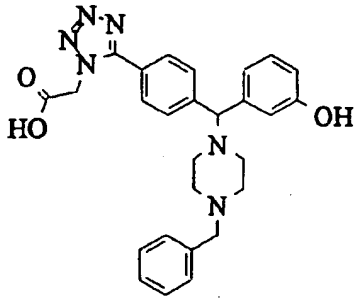
N-1 Isomer: (Example 50):

m/z: 513 (MH^+)

δ_H (400MHz, d_6-DMSO): 9.30 (1H, s), 7.68 (2H, d), 7.60 (2H, d), 7.40-7.20 (5H, m), 7.08 (1H, t), 6.84 (2H, m), 6.58 (1H, d), 5.60 (2H, s), 4.30 (1H, s), 4.06 (2H, q), 3.48 (2H, s), 2.50-2.20 (8H, m), 1.04 (3H, t).

EXAMPLE 51

(±)-2-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]-phenyl}-1-tetrazolyl)acetic acid



Aqueous sodium hydroxide (2N, 0.5ml) was added to a solution of the compound of Example 50 (70mg) in methanol (10ml) and the mixture stirred at room temperature for 18 hours. The reaction was quenched with 2N hydrochloric acid (3ml) and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide) to afford the title compound, 69mg.

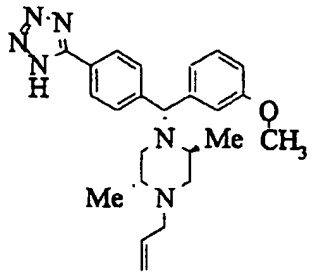
m/z: 485 (MH^+)

δ_H (400MHz, d_6-DMSO): 7.74 (2H, d), 7.60 (2H, d), 7.40-7.00 (6H, m), 6.84 (2H, m), 6.60 (1H, m), 5.14 (2H, s), 4.32 (1H, s), 3.70 (2H, s), 3.18 (1H, s), 2.70-2.30 (8H, m).

Found: C, 60.38; H, 5.80; N, 16.51. $C_{27}H_{28}N_6O_3.Na.3/2H2O.1/4NH_3$ requires C, 60.33; H, 5.73; N, 16.29%.

EXAMPLE 52

4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]phenyltetrazole



A solution of the compound of Preparation 3 (3.26g), dibutyltin oxide (780mg) and trimethylsilyl azide (2.54g) in dry toluene was stirred at 70°C under nitrogen for 48hours, after which time the reaction was quenched by the addition of 2N hydrochloric acid. The pH of the solution was adjusted to pH 10 by the addition of 0.880 ammonia solution and pre-absorption silica gel added and the solvents evaporated in vacuo. The residue was purified by column chromatography over silica gel using gradient elution (85/15/2 to 80/20/3 dichloromethane/methanol/ammonia) to afford the title compound as a brown gum, 3.28g.

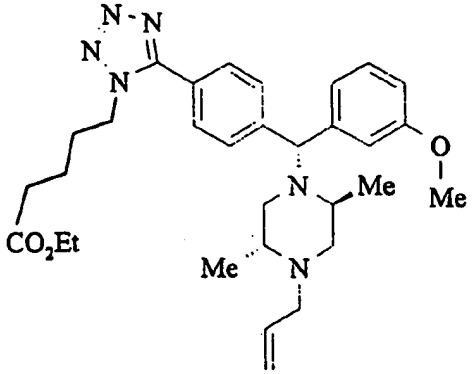
m/z: 420 (MH+)

Rf: 0.31 (80/20/3 dichloromethane/methanol/ammonia)

δ_H (300mhz, $CDCl_3$): 8.04 (2H, d), 7.43 (2H, d), 7.15 (1H, t), 6.93 (1H, bs), 6.74 (3H, m), 5.93 (1H, m), 5.32 (2H, n), 5.04 (1H, s), 3.68 (3H, s), 3.58 (1H, m), 3.28 (1H, m), 3.09 (1H, m), 2.97 (2H, m), 2.80 (1H, m), 2.55 (1H, m), 2.30 (1H, m), 1.18 (6H, 2x d).

EXAMPLE 53

Ethyl 5-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]phenyl}-1-tetrazolyl)valerate.



Phosphorus pentachloride (1.53g) was added to a solution of the compound of Preparation 36 (2.95g) in dry toluene (75ml), and the resulting mixture was stirred at 75°C for 2 hours. The solution was cooled to ambient temperature and trimethylsilyl azide (1.17g) added. The reaction mixture was maintained at ambient temperature, with stirring, for 18 hours. The solution was diluted with ethyl acetate (150ml) and washed with saturated sodium hydrogen carbonate, and the organic extracts were evaporated to dryness in vacuo. The brown residue was purified by column chromatography over silica gel (98/2; dichloromethane/methanol) to afford the title compound, 2.43g.

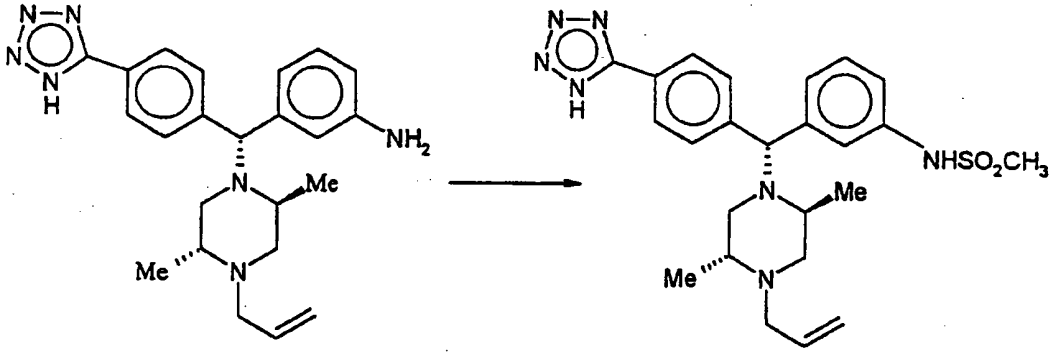
m/z: 547 (MH+)

Rf: 0.39 (95/5; dichloromethane/methanol)

δ_H (300MHz, $CDCl_3$): 7.65 (2H, d), 7.58 (2H, d), 7.25 (1H, t), 6.80 (3H, q), 5.87 (1H, m), 5.18 (3H, m), 4.42 (2H, t), 4.12 (2H, q), 3.78 (3H, s), 3.35 (1H, dd), 2.85 (2H, m), 2.60 (3H, m), 2.31 (2H, t), 2.15 (1H, m), 2.00 (3H, m), 1.68 (2H, m), 1.20 (6H, m), 1.00 (3H, d).

EXAMPLE 54

4-5-{[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methanesulphonylbenzyl]phenyl}-1H-tetrazole



To a suspension of the anilinotetrazole of Preparation 48; (600 mg; 0.0015 mole) in tetrahydrofuran was added triethylamine (161 mg; 0.0016 mole) to give a bright yellow solution. Trimethylsilyl chloride (178 mg; 0.0016 mole) was added and stirring continued for 1.5 hours. Triethylamine hydrochloride precipitated. Pyridine (468 ml; 0.0060 mole) was added followed by methanesulfonyl chloride (344 mg; 0.0030 mole) and the reaction stirred at room temperature for 18 hours. Water (10 ml) was added and

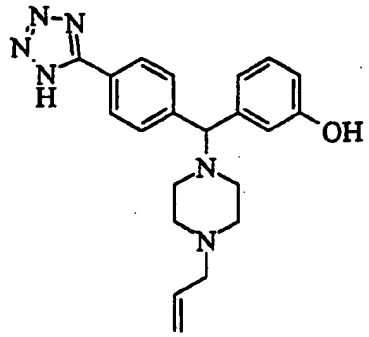
the reaction acidified to pH2 with concentrated hydrochloric acid; then basified with ammonium hydroxide solution (s.g = 0.880). The mixture was rotary evaporated to dryness and the residue re-absorbed onto silica. This was then flash chromatographed on silica; eluant 90/10/1.5 →80/20/1 CH_2Cl_2/MeOH/NH_4OH to give 220 mg of the desired product.

m/z : 483 (MH^+)

δ_H (400MHz, d_6-DMSO):7.94 (2H, d), 7.46 (2H, d), 7.32 (1H, t), 7.20 (1H, s), 7.10 (1H, d), 7.02 (1H, d), 5.80 (1H, m), 5.26 (1H, d), 5.20 (1H, d), 5.12 (1H, s), 3.36 (1H, dd), 3.18 (1H, s), 3.04 (1H, dd), 2.94 (3H, s), 2.88 (1H, d), 2.74 (1H, m), 2.68-2.56 (2H, m), 2.32 (1H, dd), 1.88 (1H, dd), 1.12 (3H, d), 1.00 (3H, d).

EXAMPLE 55

(±)-[(R,S)-α-(4-allyl-1-piperazinyl)-3-(hydroxybenzyl)phenyltetrazole



Tetraethylammonium fluoride (228mg) was added to a solution of the compound from Preparation 50 (500mg) in acetonitrile (10ml) and the reaction stirred at room temperature for 30 minutes. The reaction mixture was then evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide). This material was further purified over a polystyrene reverse phase resin, using gradient elution (90/10-50/50 water/acetonitrile). The acetonitrile was evaporated *in vacuo* and the remaining aqueous solution was frozen and lyophilised to afford the title compound as a white solid, 131mg.

m/z: 377 (MH^+)

R_f : 0.24 (70/30/3 ethyl acetate/methanol/diethylamine)

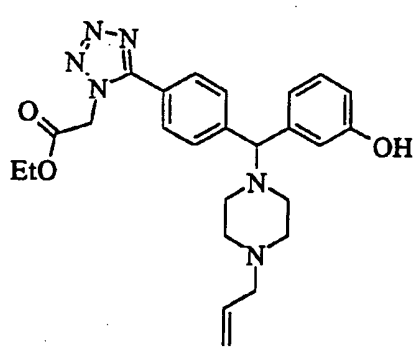
δ_H (400MHz, DMSO-d_6): 7.82 (2H, d), 7.49 (2H, d), 7.08 (1H, dd), 6.86 (2H, m), 6.58 (1H, d), 5.60 (1H, m), 5.20 (2H, m), 4.26 (1H, s), 3.10 (2H, d), 2.58 (4H, m), 2.38 (4H, m).

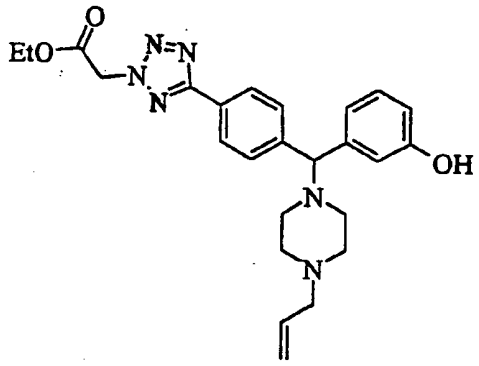
EXAMPLES 56 and 57

(±)-Ethyl-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)acetate

and

(±)-Ethyl-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl})acetate





Potassium carbonate (1.27g) and ethyl bromoacetate (344µl) were added to a solution of the compound from Preparation 50 (1.5g) in acetonitrile (60ml), and the reaction stirred under reflux for 20 hours. On cooling, water was added and the reaction mixture was extracted with ethyl acetate (3x50ml), the combined organic extracts dried (Na_2SO_4) and evaporated to dryness *in vacuo*. This material was redissolved in acetonitrile (10ml), tetraethylammonium fluoride (694mg) added and the reaction stirred at room temperatrure for an hour. Water was added and the mixture extracted with ethyl acetate (2x20ml), the combined organic extracts dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give an orange foam. The residue was purified by column chromatography over silica gel using gradient elution (70/30-100/0 ethyl acetate/hexane) to afford the N2 isomer, 270mg

m/z: 463 (MH^+)

R_f : 0.25 (ethyl acetate)

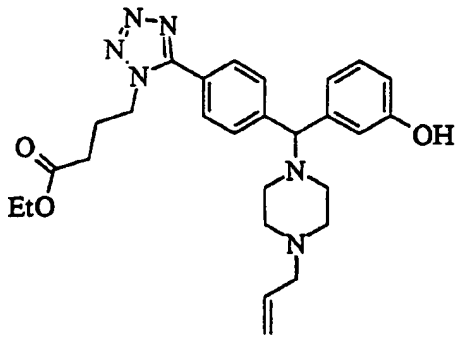
δ_H (300MHz, DMSO-d_6): 9.30 (1H, s), 7.98 (2H, d), 7.58 (2H, d), 7.06 (1H, dd), 6.85 (2H, m), 6.56 (1H, d), 5.84 (2H, s), 5.76 (1H, m), 5.10 (2H, m), 4.25 (1H, s), 4.19 (2H, q), 2.92 (2H, d), 2.34 (8H, m), 1.18 (3H, t).

and the N1 isomer, 35mg.

R_f: 0.13 (ethyl acetate)

EXAMPLE 58

(±)-Ethyl 4-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)butyrate



Tetraethylammonium fluoride (67mg) was added to a solution of the first compound in the drawings of Preparation 51 (200mg) in acetonitrile (4ml) and the reaction stirred at room temperature for 30 minutes. Water was added and the mixture extracted with ethyl acetate (3x10ml). The combined organic extracts were dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (85/15/1.5-80/20/1.5 hexane/isopropanol/ammonium hydroxide) to afford the title compound, 130mg.

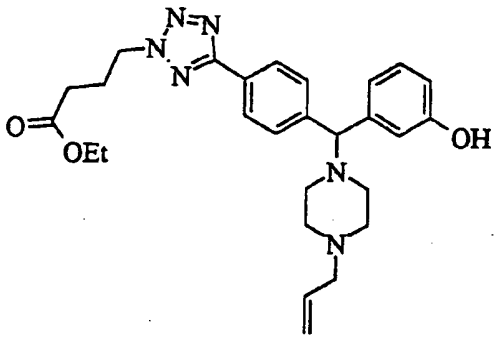
m/z: 491 (MH^+)

R_f: 0.24 (80/20/1.5 hexane/isopropanol/ammonium hydroxide)

δ_H (300MHz, $CDCl_3$): 7.60 (4H, s), 7.14 (1H, dd), 6.96 (1H, d), 6.88 (1H, s), 6.67 (1H, d), 5.86 (1H, m), 5.16 (2H, m), 4.48 (2H, t), 4.26 (1H, s), 4.02 (2H, q), 3.02 (2H, d), 2.49 (8H, m), 2.38 (2H, t), 2.24 (2H, m), 1.20 (3H, t).

EXAMPLE 59

(±)-Ethyl 4-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)butyrate



The title compound was prepared using the second compound in the drawings of Preparation 51, following a similar procedure to that described in Example 58, and was obtained in 69% yield.

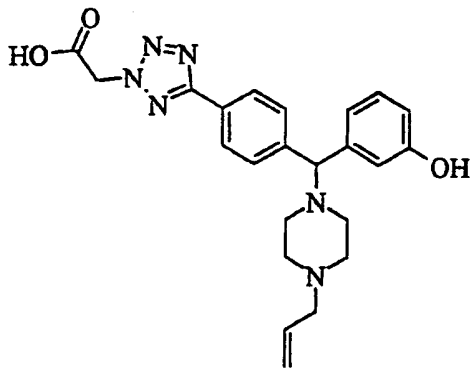
m/z: 491 (MH^+)

R_f : 0.38 (80/20/1.5 hexane/isopropanol/ammonium hydroxide)

δ_H (300MHz, DMSO-d_6): 9.29 (1H, s), 7.96 (2H, d), 7.55 (2H, d), 7.05 (1H, dd), 6.82 (2H, m), 6.54 (1H, d), 5.78 (1H, m), 5.10 (2H, m), 4.74 (2H, t), 4.22 (1H, s), 4.00 (2H, q), 2.90 (2H, d), 2.35 (10H, m), 2.18 (2H, m), 1.14 (3H, t).

EXAMPLE 60

(±)-(5-{4-(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)acetic acid



2N aqueous sodium hydroxide solution (1ml) was added to a solution of the compound of Example 57 (250mg) in methanol (2ml) and dioxan (4ml), and the reaction stirred at room temperature for an hour. The pH of the reaction was adjusted to 5 using 2N aqueous hydrochloric acid and the mixture evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (70/30/3 ethyl acetate/methanol/ammonium hydroxide), and this material was further purified over a polystyrene reverse phase resin using gradient elution (80/20-50/50 water/acetonitrile). The acetonitrile was evaporated *in vacuo* and the remaining aqueous solution was frozen and lyophilised to afford the title compound as a white solid, 190mg.

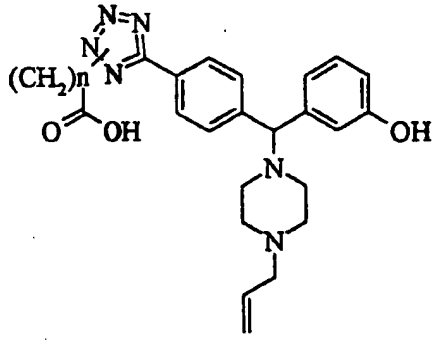
m/z: 435 (MH^+)

R_f : 0.2 (80/20/3 dichloromethane/methanol/ammonium hydroxide)

δ_H (300MHz, DMSO-d_6): 9.40 (1H, br.s), 7.99 (2H, d), 7.57 (2H, d), 7.08 (1H, dd), 6.84 (2H, m), 6.58 (1H, d), 5.83 (1H, m), 5.47 (2H, s), 5.26 (2H, m), 4.30 (1H, s), 3.28 (2H, d), 2.74 (4H, m), 2.40 (4H, m).

EXAMPLES 61 to 63

The following compounds of the general formula:



were prepared by hydrolysis of the corresponding esters, Examples 56, 58 and 59, by similar methods to that used in Example 60.

Ex	Isomer	n	*m/z*	R_f(*a*)	^{1}Hnmr/Analytical data
61	1	1	435	0.26	δ_H (300MHz, DMSO-d_6): 9.40 (1H, br.s), 7.74 (2H, d), 7.59 (2H, d), 7.08 (1H, dd), 6.84 (2H, m), 6.59 (1H, d) 5.80 (1H, m), 5.24 (2H, m), 5.08 (2H, s), 4.30 (1H, s), 3.22 (2H, d), 2.68 (4H, m), 2.36 (4H, m).
62	1	3	463	0.18	δ_H (300MHz, DMSO-d_6): 7.72 (2H, d), 7.60 (2H, d), 7.07 (1H, dd), 6.84 (2H, m), 6.57 (1H, d), 5.76 (1H, m), 5.10 (2H, m), 4.45 (2H, t), 4.29 (1H, s), 3.28 (1H, br.s), 2.92 (2H, d), 2.36 (8H, m), 2.25 (2H, t), 2.01 (2H, m). Found: C, 61.26; H, 6.31; N, 16.64. $C_{25}H_{30}N_6O_3.16/10H_2O$ requires C, 61.11; H, 6.81; N, 17.10%
63	2	3	463	0.24	δ_H (400MHz, DMSO-d_6): 9.32 (1H, br.s), 7.98 (2H, d), 7.58 (2H, d), 7.07 (1H, dd), 6.84 (2H, m), 6.58 (1H, d), 5.78 (1H, m), 5.12 (2H, m), 5.74 (2H, t), 4.24 (1H, s), 2.92 (2H, d), 2.34 (10H, m), 2.14 (2H, m). Found: C, 62.83; H, 6.40; N, 17.63. $C_{25}H_{30}N_6O_3.3/4H_2O$ requires C, 63.07; H, 6.67; N, 17.65%

(*a*): 80/20/3 dichloromethane/methanol/ammonium hydroxide

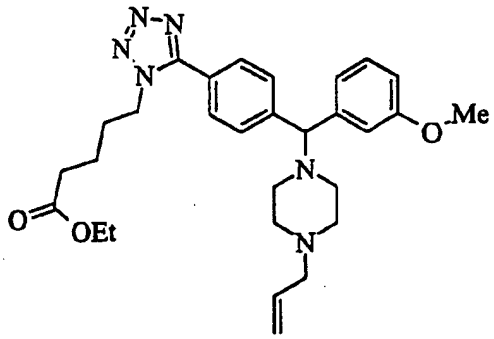
Example 61. (±)-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)acetic acid.

Example 62. (±)-4-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)butyric acid.

Example 63. (±)-4-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)butyric acid.

EXAMPLE 64

(±)-Ethyl 5-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-methoxybenzyl]phenyl}-1-tetrazolyl)valerate hydrochloride



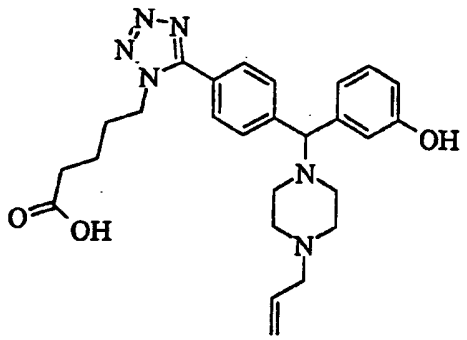
A solution of the compound from Preparation 57 (582mg) and phosphorus pentachloride (368mg) in dry toluene (30ml), was stirred at 70°C for 90 minutes. On cooling, trimethylsilyl azide (785µl) was added and the reaction stirred at room temperature for 72 hours. Saturated aqueous sodium hydrogen carbonate solution was added and the mixture extracted with ethyl acetate (3x30ml). The combined organic extracts were washed with water and brine, then dried (Na_2SO_4), and evaporated to dryness *in vacuo*, to give a brown gum. The residue was purified by column chromatography over silica gel (80/20/1.5 hexane/isopropanol/ammonium hydroxide), to afford the title compound, 218mg.

m/z: 519 (MH^+)

δ_H (300MHz, $CDCl_3$): 8.17 (2H, d), 7.78 (2H, d), 7.59 (1H, s), 7.37 (2H, m), 6.92 (1H, d), 6.12 (1H, m), 5.60 (2H, m), 5.08 (1H, s), 4.40 (2H, t), 4.22 (2H, m), 4.08 (2H, q), 3.94 (2H, m), 3.86 (3H, s), 3.68 (2H, d), 3.52 (4H, m), 2.30 (2H, t), 1.99 (2H, m), 1.64 (2H, m), 1.22 (3H, t).

EXAMPLE 65

(±)-5-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid.



A solution of boron tribromide in dichloromethane (10.5ml, 1M) was added dropwise to a solution of the compound of Example 64 (2.73g), in dichloromethane (25ml) and the reaction stirred under a nitrogen atmosphere at room temperature for 6 hours. Aqueous saturated sodium hydrogen carbonate solution was added and the mixture extracted with dichloromethane (3x50ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*, to give a brown foam.

A solution of this material in dioxan (10ml), methanol (5ml) and 2N aqueous sodium hydroxide solution (3ml) was stirred at room temperature for 20 hours. The mixture was acidified using 2N hydrochloric acid, then basified using ammonium hydroxide solution, and the mixture evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide) and was further purified over a polystyrene reverse phase resin using gradient elution (100/0-0/100 water/acetonitrile). The acetonitrile was evaporated *in vacuo* and the remaining aqueous solution was frozen and lyophilised to afford the title compound as a white solid, 238mg.

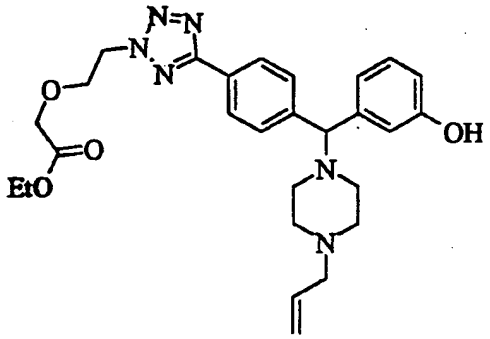
m/z: 477 (MH^+)

δ_H (300MHz, DMSO-d_6): 10.50 (1H, br.s), 7.70 (2H, d), 7.61 (2H, d), 7.08 (1H, dd), 6.84 (2H, m), 6.57 (1H, d), 5.79 (1H, m), 5.12 (2H, m), 4.44 (2H, t), 4.33 (1H, s), 3.20 (1H, br.s), 2.94 (2H, d), 2.40 (4H, m), 2.34 (4H, m), 2.15 (2H, t), 1.82 (2H, m), 1.44 (2H, m).

Found: C, 63.60; H, 6.83; N, 17.05. $C_{26}H_{32}N_6O_3.4/5H_2O$ requires C, 63.60; H, 6.90; N, 17.12%

EXAMPLE 66

(±)-Ethyl 2-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-(hydroxybenzyl)phenyl]-2-tetrazolyl})ethoxyacetate



An ice-cooled solution of the compound of Preparation 59 (1.6g) in ethanol (50ml) was saturated with hydrogen chloride gas and stirred for 45 minutes. The reaction mixture was evaporated to dryness *in vacuo*, to give a white solid. A solution of this material in ethanol (5ml), was cooled to 0°C, and water (5ml) added. The resulting solution was stirred at 0°C for 90 minutes, ammonium hydroxide solution added and the mixture extracted with dichloromethane (2x25ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*, to give a white foam. The residue was purified by column chromatography over silica gel (95/5/0.5 dichlorometahne/methanol/ammonium hydroxide) to afford the title compound, 1.24g.

m/z: 507 (MH^+)

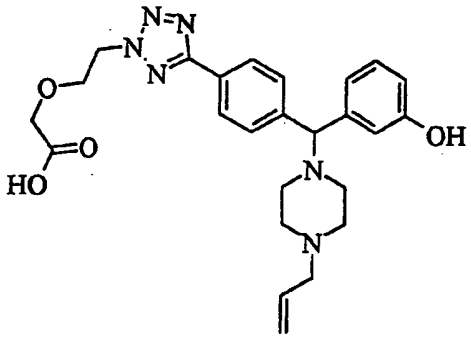
R_f : 0.59 (90/10/1 diethyl ether/ethanol/ammonium hydroxide)

δ_H (400MHz, $CDCl_3$): 8.07 (2H, d), 7.54 (2H, d), 7.15 (1H, dd), 6.98 (1H, d), 6.90 (1H, s), 6.66 (1H, d), 6.14 (1H, br.s), 5.88 (1H, m), 5.18 (2H, m), 4.87 (2H, t), 4.19 (5H, m), 4.08 (2H, s), 3.04 (2H, d), 2.52 (8H, m), 1.26 (3H, t).

Found: C, 63.38; H, 6.69; N, 16.46. $C_{27}H_{34}N_6O_4.1/5H_2O$ requires C, 63.56; H, 6.80; N, 16.47%

EXAMPLE 67

(±)-2-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)ethoxyacetic acid



The title compound was prepared using the compound of Example 66, following a similar method to that described in Example 60, and was obtained as a white solid, in 63% yield.

m/z: 479 (MH^+)

R_f : 0.2 (80/20/3 dichloromethane/methanol/ammonium hydroxide)

δ_H (400MHz, $CDCl_3$): 9.29 (1H, br.s), 7.94 (2H, d), 7.54 (2H, d), 7.06 (1H, dd), 6.81 (2H, m), 6.54 (1H, d), 5.75 (1H, m), 5.09 (2H, m), 4.86 (2H, t), 4.22 (1H, s), 4.00 (2H, t), 3.95 (2H, s), 3.54 (1H, s), 2.90 (2H, d), 2.34 (8H, m).

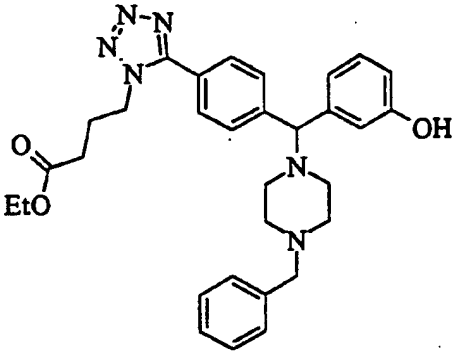
Found: C, 59.42; H, 6.14; N, 16.31. $C_{25}H_{30}N_6O_4.3/2H_2O$ requires C, 59.39; H, 6.58; N, 16.62%

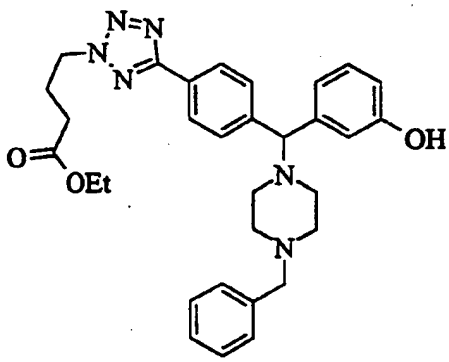
EXAMPLES 68 and 69

(±)-Ethyl-4-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)butyrate

and

(±)-Ethyl 4-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)butyrate





A suspension of the compound of Preparation 4b (1.62g), potassium carbonate (1.25g) and ethyl 4-bromobutyrate (430µl) in acetonitrile (25ml) was stirred under reflux for 18 hours. On cooling, the reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water. The phases were separated, the aqueous layer extracted with further ethyl acetate, and the combined organic extracts dried ($MgSO_4$) and evaporated to dryness *in vacuo*, to give a yellow gum. Tetraethylammonium fluoride (0.8g) was added to a solution of this material in tetrahydrofuran (20ml) and the solution stirred at room temperature for 4 hours. The reaction mixture was concentrated *in vacuo*, and the residue partitioned between ethyl acetate and aqueous ammonium chloride solution. The phases were separated, the aqueous layer extracted with further ethyl acetate, and the combined organic extracts dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (50/50 ethyl acetate/hexane), to afford the N2 isomer, 1.02g.

m/z: 542 ($M2H^+$)

δ_H (400MHz, DMSO-d_6): 9.29 (1H, s), 7.97 (2H, d), 7.55 (2H, d), 7.26 (5H, m), 7.06 (1H, dd), 6.68 (2H, m), 6.57 (1H, d), 4.74 (2H, t), 4.28 (1H, s), 4.02 (2H, q), 3.46 (2H, s), 2.30-2.48 (8H, m), 2.19 (2H, m), 1.14 (3H, t).

followed by the N1 isomer, 0.14g.

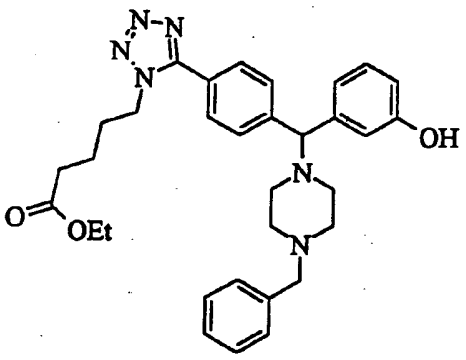
m/z: 542 ($M2H^+$)

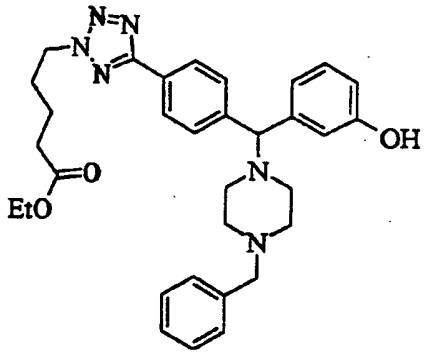
δ_H (400MHz, DMSO-d_6): 9.30 (1H, s), 7.72 (2H, d), 7.62 (2H, d), 7.26 (5H, m), 7.07 (1H, dd), 6.84 (2H, m), 6.58 (1H, d), 4.48 (2H, t), 4.32 (1H, s), 3.92 (2H, q), 3.47 (2H, s), 2.22-2.44 (8H, m), 2.05 (2H, m), 1.08 (3H, t).

EXAMPLE 70 and 71

(±)-Ethyl-5-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valerate and

(±)-Ethyl 5-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]-phenyl}-2-tetrazolyl)valerate





The title compounds were prepared following the procedure described in Example 68 and 69, using the compound of Preparation 4b, ethyl 5-bromovalerate, and were obtained in 10% and 56% yield respectively.

N1 isomer,

m/z: 555 (MH^+)

δ_H (400MHz, DMSO-d_6): 9.32 (1H, s), 7.72 (2H, d), 7.61 (2H, d), 7.28 (5H, m), 7.08 (1H, dd), 6.84 (2H, m), 6.58 (1H, d), 4.45 (2H, t), 4.30 (1H, s), 3.97 (2H, q), 3.47 (2H, s), 2.31-2.46 (8H, m), 2.23 (2H, t), 1.81 (2H, m), 1.46 (2H, m), 1.12 (3H, t).

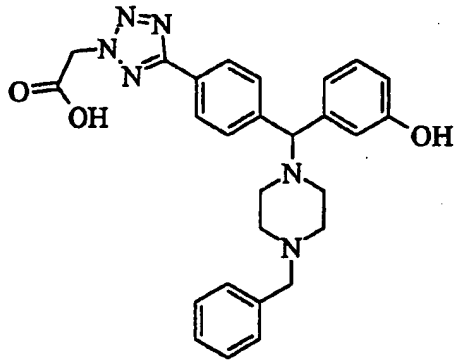
and the N2 isomer.

m/z: 555 (MH^+)

δ_H (400MHz, DMSO-d_6): 9.29 (1H, s), 7.97 (2H, d), 7.56 (2H, d), 7.27 (5H, m), 7.06 (1H, dd), 6.83 (2H, m), 6.57 (1H, d), 4.70 (2H, t), 4.27 (1H, s), 4.03 (2H, q), 3.48 (2H, s), 2.26-2.48 (8H, m), 1.98 (2H, m), 1.52 (2H, m), 1.16 (3H, t).

EXAMPLE 72

(±)-{5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)acetic acid



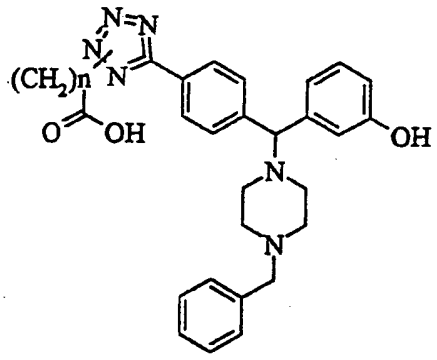
2N aqueous sodium hydroxide solution (1.05ml) was added to a solution of the compound from Example 49 (540mg) in methanol (15ml), and the reaction stirred at room temperature for 2 hours. The reaction mixture was acidified to pH 6 using 2N hydrochloric acid and then evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide) to afford the title compound as a colourless foam, 340mg.

m/z: 485 (MH^+)

δ_H (300MHz, DMSO-d_6): 7.97 (2H, d), 7.55 (2H, d), 7.30 (5H, m), 7.04 (1H, dd), 6.82 (2H, m), 6.56 (1H, d), 5.36 (2H, s), 4.28 (1H, s), 3.62 (2H, s), 2.30-2.62 (8H, m).

EXAMPLES 73 to 76

The following compounds of the general formula:



were prepared by hydrolysis of the corresponding esters, by similar methods to that used in Example 72

Ex	Isomer	n	*m/z*	^{1}H-nmr
73	1	3	513	δ_H (400MHz, DMSO-d_6): 7.74 (2H, d), 7.62 (2H, d), 7.26 (5H, m), 7.08 (1H, dd), 6.85 (2H, m), 6.58 (1H, d), 4.48 (2H, t), 4.30 (1H, s), 3.48 (2H, s), 2.50 (4H, m), 2.38 (6H, m), 2.00 (2H, m).
74	2	3	513	δ_H (400MHz, DMSO-d_6): 7.98 (2H, d), 7.55 (2H, d), 7.27 (5H, m), 7.07 (1H, dd), 6.84 (2H, m), 6.58 (1H, d), 4.73 (2H, t), 4.26 (1H, s), 3.45 (2H, s), 2.37 (8H, m), 2.16 (4H, m).
75	1	4	527	δ_H (300MHz, DMSO-d_6): 7.70 (2H, d), 7.60 (2H, d), 7.26 (5H, m), 7.08 (1H, dd), 6.83 (2H, m), 6.57 (1H, d), 4.43 (2H, t), 4.30 (1H, s), 3.45 (2H, s), 2.38 (8H, m), 2.18 (2H, t), 1.81 (2H, m), 1.44 (2H, m).
76	2	4	527	δ_H (300MHz, DMSO-d_6): 7.84 (2H, d), 7.52 (2H, d), 7.23 (5H, m), 7.04 (1H, dd), 6.90 (2H, m), 6.54 (1H, d), 4.68 (2H, t), 4.24 (1H, s), 3.43 (2H, s), 2.36 (8H, m), 2.17 (2H, t), 1.92 (2H, m), 1.46 (2H, m).

Example 73 . (±)-4-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)butyric acid

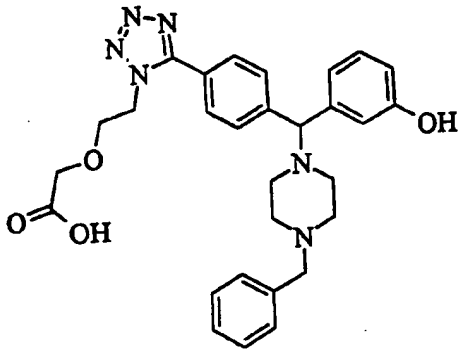
Example 74 . (±)-4-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)butyric acid

Example 75 . (±)-5-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid

Example 76 . (±)-5-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valeric acid

EXAMPLE 77

(±)-2-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)ethoxyacetic acid



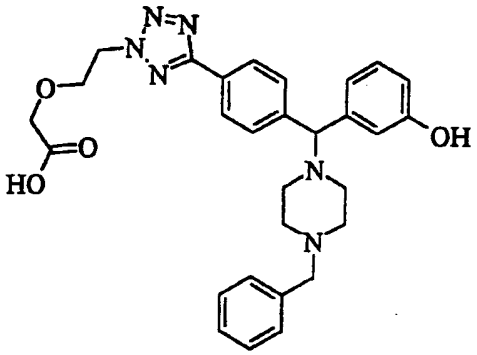
Hydrogen chloride gas was passed through a solution of the first compound in the drawings of Preparation 60 (180mg) in ethanol (10ml) and the reaction stirred at room temperature for an hour. The reaction mixture was then evaporated to dryness *in vacuo*, to give a colourless foam. This material was dissolved in aqueous ethanol (15ml), sodium hydroxide (40mg) added, and the reaction stirred at room temperature for 72 hours. The reaction mixture was acidified to pH 3.5 using 2N hydrochloric acid solution, rebasified with ammonium hydroxide solution, and the mixture evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide) to afford the title compound as a colourless foam, 150mg.

R_f: 0.37 (80/20/3 dichloromethane/methanol/ammonium hydroxide)

δ_H (400MHz DMSO-d_6): 7.80 (2H, d), 7.58 (2H, d), 7.26 (5H, m), 7.05 (1H, dd), 6.82 (2H, m), 6.56 (1H, d), 4.56 (2H, t), 4.28 (1H, s), 3.86 (2H, t), 3.74 (2H, s), 3.46 (2H, s), 2.20-2.45 (8H, m).

EXAMPLE 78

(±)-2-(5-{4-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)ethoxyacetic acid



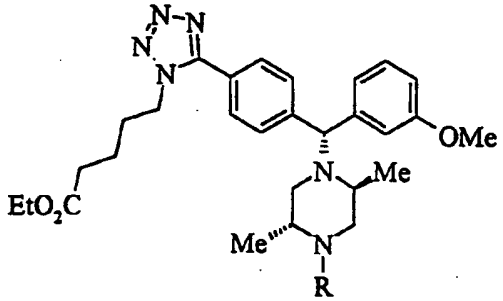
The title compound was prepared using the second compound in the drawings of Preparation 60, following the method described for Example 77, and was obtained as a colourless foam, (65%).

R_F: 0.34 (80/20/3 dichloromethane/methanol/ammonium hydroxide)

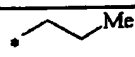
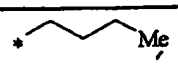
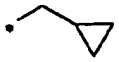
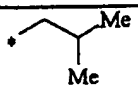
δ_H (400MHz, DMSO-d_6): 7.97 (2H, d), 7.55 (2H, d), 7.26 (5H, m), 7.05 (1H, dd), 6.82 (2H, m), 6.55 (1H, d), 4.85 (2H, t), 4.24 (1H, s), 4.00 (2H, t), 3.80 (2H, s), 3.45 (2H, s), 2.20-2.45 (8H, m).

EXAMPLES 79 to 82

The following compounds of the general formula:



were prepared from the corresponding amides (Preparations 62 to 65) by similar methods to that described for Example 53.

Ex	R	*m/z* (MH^+)	nmr
79		549	δ_H (400MHz, $CDCl_3$): 7.68 (2H, d), 7.60 (2H, d), 7.26 (1H, m), 6.90-6.72 (3H, m), 5.24 (1H, s), 4.42 (2H, m), 4.12 (2H, m), 3.80 (3H, s), 2.88 (1H, d), 2.76-2.46 (4H, m), 2.34 (2H, t), 2.20 (2H, m), 2.02 (2H, m), 1.94 (1H, m), 1.76-1.40 (4H, m), 1.30-1.20 (6H, m), 1.00 (3H, d), 0.90 (3H, t).
80		563	δ_H (400MHz, $CDCl_3$): 7.66 (2H, d), 7.60 (2H, d), 7.24 (1H, m), 6.88-6.72 (3H, m), 5.24 (1H, s), 4.42 (2H, m), 4.12 (2H, m), 3.80 (3H, s), 2.86 (1H, d), 2.72-2.42 (4H, m), 2.38-1.88 (7H, m), 1.68 (2H, m), 1.42 (2H, m), 1.38-1.08 (8H, m), 1.00 (3H, d), 0.92 (3H, t).
81		561	δ_H (400MHz, DMSO-d_6): 7.72 (2H, d), 7.60 (2H, d), 7.28 (1H, m), 6.86 (3H, m), 5.18 (1H, br s), 4.46 (2H, t), 4.00 (2H, q), 3.74 (3H, s), 2.90 (1H, d), 2.60 (3H, m), 2.40-2.10 (4H, m), 1.80 (3H, m), 1.40 (2H, m), 1.20-1.10 (6H, m), 0.90 (3H, d), 0.76 (1H, m), 0.40 (2H, m), 0.02 (2H, m).
82		563	δ_H (400MHz, DMSO-d_6): 7.72 (2H, d), 7.62 (2H, d), 7.24 (1H, t), 6.98-6.80 (3H, m), 5.02 (1H, br s), 4.44 (2H, t), 3.98 (2H, q), 3.72 (3H, s), 2.80 (1H, d), 2.70-2.50 (4H, m), 2.38-1.40 (11H, m), 1.20-1.06 (5H, m), 0.96 (3H, d), 0.82 (3H, d), 0.78 (3H, d).

Example 79: Ethyl 5-(5-{4-[(R)-α-(2(S),5(R)-4-propyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]phenyl}-1-tetrazolyl)valerate.

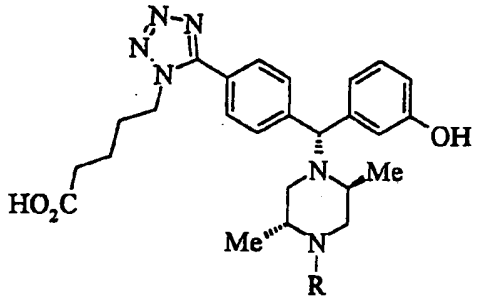
Example 80: Ethyl 5-(5-{4-[(R)-α-(2(S),5(R)-4-butyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]phenyl}-1-tetrazolyl)valerate.

Example 81: Ethyl 5-(5-{4-[(R)-α-(2(S),5(R)-4-cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]phenyl}-1-tetrazolyl)valerate.

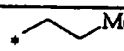
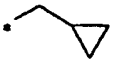
Example 82: Ethyl 5-(5-{4-[(R)-α-(2(S),5(R)-4-*iso*-butyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]phenyl}-1-tetrazolyl)valerate.

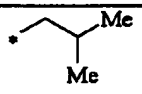
EXAMPLES 83 to 86

The following compounds of the general formula:



were prepared from the corresponding esters (Examples 79 to 82) by similar methods to that described for Example 36.

Ex	R	*m/z* (MH^+)	Data
83		507	δ_H (400MHz, DMSO-d_6): 7.72 (2H, d), 7.60 (2H, d), 7.12 (1H, m), 6.80-6.60 (3H, m), 5.04 (1H, br s), 4.44 (2H, t), 3.36 (2H, br s), 2.80 (1H, d), 2.70-2.40 (6H, m), 2.20-2.06 (3H, m), 1.84 (2H, m), 1.46 (2H, m), 1.38 (2H, m), 1.10 (3H, d), 0.94 (3H, d), 0.80 (3H, t). *m/z*: 507 (MH^+) Found: C, 64.10; H, 7.34; N, 16.06. $C_{28}H_{38}N_6O_3.H_2O$ requires C, 64.10; H, 7.68; N, 16.02% $[\alpha]_D$ +18.9° (c=0.13, methanol)
84		521	δ_H (400MHz, DMSO-d_6): 7.72 (2H, d), 7.60 (2H, d), 7.14 (1H, t), 6.80-6.60 (3H, m), 5.02 (1H, s), 4.48 (2H, t), 3.30 (2H, br s), 2.80 (1H, d), 2.70-2.40 (4H, m), 2.24-2.02 (4H, m), 1.86 (3H, m), 1.46 (2H, m), 1.36 (2H, m), 1.24 (2H, m), 1.08 (3H, d), 0.96 (3H, t), 0.84 (3H, t). *m/z*: 521 (MH^+) Found: C, 65.70; H, 7.90; N, 16.00. $C_{29}H_{40}N_6O_3.0.5H_2O$ requires C, 65.76; H, 7.80; N, 15.87% $[\alpha]_D$ +14.5° (c=0.12, methanol)
85		519	δ_H (400MHz, DMSO-d_6): 7.72 (2H, d), 7.60 (2H, d), 7.14 (1H, m), 6.76-6.60 (3H, m), 5.10 (1H, br s), 4.44 (2H, t),

Ex	R	*m/z* (MH^+)	Data
			3.30 (2H, br s), 2.92 (1H, m), 2.70-2.00 (8H, m), 1.80 (3H, m), 1.42 (2H, m), 1.12 (3H, d), 0.90 (3H, d), 0.76 (1H, m), 0.40 (2H, m), 0.02 (2H, m). *m/z*: 519 (MH^+) Found: C, 64.34; H, 7.10; N, 15.42. $C_{29}H_{38}N_6O_3.1.25H_2O$ requires C, 64.36; H, 7.54; N, 15.53%
86		521	δ_H (400MHz, DMSO-d_6): 7.70 (2H, d), 7.60 (2H, d), 7.10 (1H, t), 6.80-6.60 (3H, m), 4.96 (1H, br s), 4.44 (2H, t), 3.30 (2H, br s), 2.80 (1H, d), 2.66 (1H, m), 2.58 (1H, m), 2.30-2.10 (3H, m),2.02 (1H, m), 1.94-1.76 (4H, m), 1.64 (1H, m), 1.42 (3H, m), 1.10 (3H, d), 0.96 (3H, d), 0.94 (3H, d), 0.82 (3H, d), 0.78 (3H, d). *m/z*: 521 (MH^+) Found: C, 64.70; H, 7.46; N, 15.43. $C_{29}H_{40}N_6O_3.1.0H_2O$ requires C, 64.66; H, 7.86; N, 15.60%

Example 83: (+)-5-(5-{4-[(R)-α-(2(S),5(R)-4-propyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid.

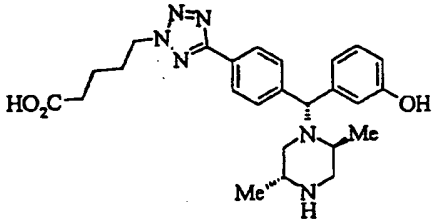
Example 84: (+)-5-(5-{4-[(R)-α-(2(S),5(R)-4-butyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid.

Example 85: 5-(5-{4-[(R)-α-(2(S),5(R)-4-cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid.

Example 86: 5-(5-{4-[(R)-α-(2(S),5(R)-4-*iso*-butyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid.

EXAMPLE 87

5-(5-{4-[(R)-α-(2(S),5(R)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valeric acid.



Tris(triphenylphosphine)rhodium(I) chloride (200mg) was added to a solution of the compound of Example 42 (500mg) in acetonitrile (160ml) and water (40ml). The reaction mixture was heated under a gentle reflux and the solvent allowed to distil off slowly. Additional acetonitrile/water (200ml; 4:1 v/v) was added at such a rate as to maintain a steady distillation. After the addition of solvent was complete the distillation was continued until the volume was reduced to approximately 60ml. The cooled solution was poured into ethyl acetate and washed with saturated aqueous sodium bicarbonate solution and saturated brine. The solution was dried (magnesium sulphate), evaporated to dryness *in vacuo* and the residue was purified by column chromatography over silica gel (70/30/4 dichloromethane/methanol/ammonium hydroxide) to afford the title compound, 360mg.

m/z: 465 (MH^+)

R_f: 0.09 (80/20/3 dichloromethane/methanol/ammonium hydroxide)

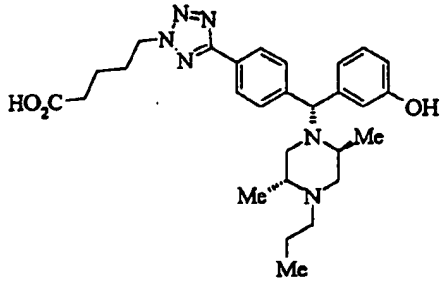
δ_H (400MHz, DMSO-d_6): 7.98 (2H, d), 7.50 (2H, d), 7.16 (1H, t), 6.74-6.50 (3H, m), 5.26 (1H, s), 4.70 (2H, t), 3.30 (2H, br), 2.84 (1H, d), 2.60-2.18 (4H, m), 1.96 (1H, m), 1.66-1.40 (3H, m), 1.10 (3H, d), 0.86 (3H, d).

m/z: 465 (MH^+)

Found: C, 62.71; H, 7.14; N, 16.95. $C_{25}H_{32}N_6O_3.1.0H_2O$ requires C, 62.22; H, 7.10; N, 17.41%

EXAMPLE 88

(+)-5-(5-{4-[(R)-α-(2(S),5(R)-4-propyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valeric acid.



To a solution of the compound of Example 87 (350mg), propionaldehyde (102µl) and glacial acetic acid (53µl) in dry dimethylformamide (20ml) was added, with stirring, sodium triacetoxyborohydride (486mg). The resulting mixture was stirred at room temperature for 18 hours after which time it was evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol) to afford the title compound as beige solid. The compound was further purified over reverse phase polystyrene resin (100% water to 100% acetonitrile in 10% increments) to afford, after freeze-drying, the title compound as a flocculant white powder, 273mg.

m/z: 507 (MH^+)

R_f: 0.18 (80/20/3 dichloromethane/methanol/ammonium hydroxide)

δ_H (400MHz, DMSO-d_6): 7.97 (2H, d), 7.56 (2H, d), 7.12 (1H, t), 6.74-6.50 (3H, m), 4.95 (1H, s), 4.70 (2H, t), 2.77 (1H, d), 2.68-2.37 (4H, m), 2.21 (2H, t), 2.08 (2H, m), 1.90 (3H, m), 1.49 (2H, m), 1.35 (2H, m), 1.08 (3H, d), 0.90 (3H, d), 0.80 (3H, d).

Found: C, 64.17; H, 7.63; N, 16.07. $C_{28}H_{38}N_6O_3.1.0H_2O$ requires C, 64.10; H, 7.68; N, 16.02%

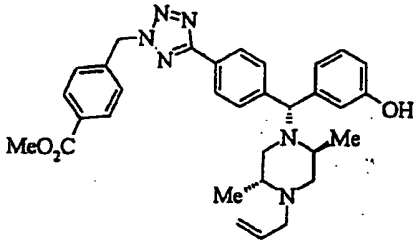
$[\alpha]_D$ +17.6° (c=0.106, methanol)

EXAMPLES 89 and 90

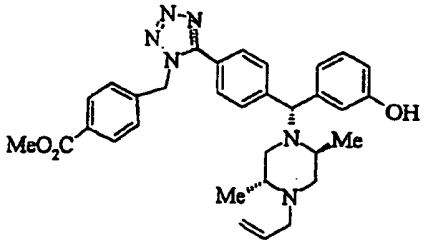
Methyl (5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)-4-methylbenzoate.

and

Methyl (5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)-4-methylbenzoate.



and



A solution of the compound of Preparation 31 (1.07g), potassium carbonate (855mg) and methyl 4-(bromomethyl)benzoate (544mg) in dry acetonitrile (15ml) was heated under reflux for 18 hours. To the cooled mixture was added tetraethylammonium fluoride (462mg) and the resulting mixture stirred for 30 minutes and the concentrated to a volume of 3ml *in vacuo*. The residue was partitioned between ethyl acetate and 2% aqueous sodium hydrogen carbonate solution, and the layers separated. The aqueous phase was extracted with further ethyl acetate and the combined organics dried (magnesium sulphate) and evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel using gradient elution (85/15/1 to 80/20/1.5 pentane/isopropanol/ammonium hydroxide) to afford the N-2 isomer, 605mg

R_f: 0.21 (85/15/1 pentane/isopropanol/ammonium hydroxide)

δ_H (300MHz, $CDCl_3$): 8.00 (2H, d), 7.57 (2H, d), 7.43 (1H, m), 6.80-6.60 (3H, m), 5.98-5.80 (1H, m), 5.25-5.05 (3H, m), 4.95 (1H, s), 3.90 (3H, s), 3.43-3.33 (1H, m), 3.00-2.43 (5H, m), 2.23-2.03 (1H, m), 2.02-1.93 (1H, m), 1.17 (3H, d), 1.00 (3H, d).

followed by the N-1 isomer, 160mg.

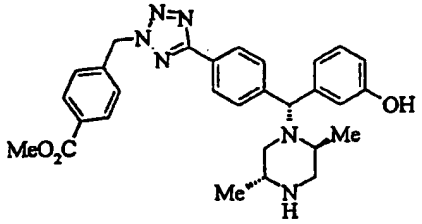
R_f: 0.10 (85/15/1 pentane/isopropanol/ammonium hydroxide)

δ_H (300MHz, $CDCl_3$): 7.98 (2H, d), 7.53 (2H, d), 7.43 (1H, m), 7.23-7.10 (3H, m), 6.73 (2H, m), 6.57 (1H, s), 5.93-5.77 (1H, m), 5.25-5.05 (3H, m), 4.95 (1H, s), 3.90 (3H, s), 3.43-3.33 (1H, m), 3.00-2.43 (5H, m), 2.23-2.03 (1H, m), 2.02-1.93 (1H, m), 1.17 (3H, d), 1.00 (3H, d).

EXAMPLE 91

Methyl (5-{4-[(R)-α-(2(S),5(R)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)-4-methylbenzoate.

The compound of the following formula:



was prepared by a similar method to that described for Preparation 61 using the compound of Example 89.

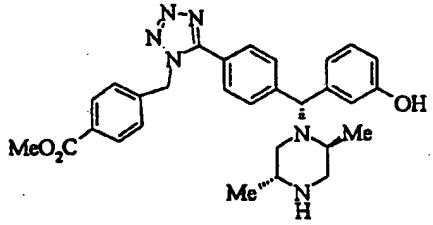
Rf: 0.08 (9/1; dichloromethane/methanol)

δ_H (400MHz, $CDCl_3$): 8.00 (4H, m), 7.63 (1H, m), 7.55-7.35 (4H, m), 7.15 (1H, m), 6.67-6.63 (2H, m), 6.60 (1H, s), 5.80 (2H, m), 5.25 (1H, m), 3.88 (3H, s), 2.90 (2H, m), 2.63 (2H, m), 2.43 (1H, br s), 2.00 (1H, m), 1.65 (1H, m), 1.10 (3H, d), 0.90 (3H, d).

EXAMPLE 92

Methyl (5-{4-[(R)-α-(2(S),5(R)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)-4-methylbenzoate.

The compound of the following formula:



was prepared by a similar method to that described for Preparation 61 using the compound of Example 90.

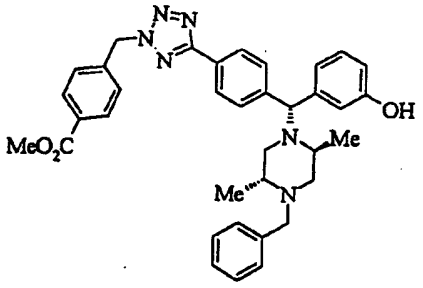
Rf: 0.05 (9/1; dichloromethane/methanol)

δ_H (400MHz, $CDCl_3$): 7.97 (2H, m), 7.67 (2H, m), 7.57-7.38 (4H, m), 7.15 (1H, m), 6.78 (1H, m), 6.65 (1H, m), 6.52 (1H, br s), 5.65 (2H, s), 5.28 (1H, m), 3.90 (3H, s), 2.90 (2H, m), 2.67 (1H, m), 2.53 (1H, m), 2.38 (1H, br s), 1.97 (1H, m), 1.62 (1H, m), 1.13 (3H, d), 0.93 (3H, d).

EXAMPLE 93

Methyl (5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)-4-methylbenzoate.

The compound of the following formula:



was prepared by reductive alkylation of the compound of Example 91 with benzaldehyde using a method similar to that described for Preparation 8.

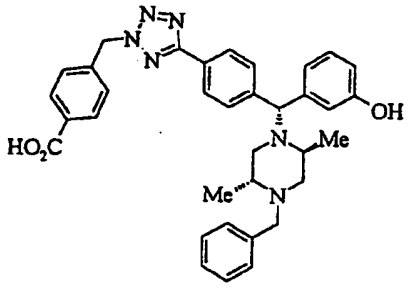
Rf: 0.27 (96/4; dichloromethane/methanol)

δ_H (400MHz, $CDCl_3$): 8.07 (4H, m), 7.53 (2H, m), 7.43 (2H, m), 7.35-7.10 (6H, m), 6.83-6.65 (3H, m), 5.83 (2H, s), 5.10 (1H, m), 4.83 (1H, br s), 3.90 (3H, s), 3.87 (1H, br d), 3.23 (1H, br d), 2.77-2.50 (4H, m), 2.08-1.93 (2H, m), 1.10 (6H, m).

EXAMPLE 94

(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)-4-methylbenzoic acid.

The compound of the following formula:



was prepared by hydrolysis of the compound of Example 93 using a method similar to that described for Example 19.

Rf: 0.40 (76/20/4; dichloromethane/methanol/ammonium hydroxide)

m/z: 589 (MH^+)

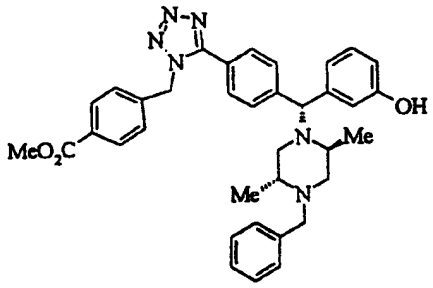
δ_H (400MHz, DMSO-d_6): 8.00-7.85 (4H, m), 7.50 (2H, m), 7.38 (2H, m), 7.30-7.03 (6H, m), 6.77-6.60 (3H, m), 6.02 (2H, s), 4.95 (1H, m), 3.75 (1H, br d), 3.27 (1H, br d), 2.73-2.27 (4H, m), 2.03-1.87 (2H, m), 1.00 (6H, m).

Found: C, 66.86; H, 6.06; N, 13.12. $C_{35}H_{36}N_6O_3.2.25H_2O$ requires C, 66.80; H, 6.49; N, 13.35%

EXAMPLE 95

Methyl (5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)-4-methylbenzoate.

The compound of the following formula:



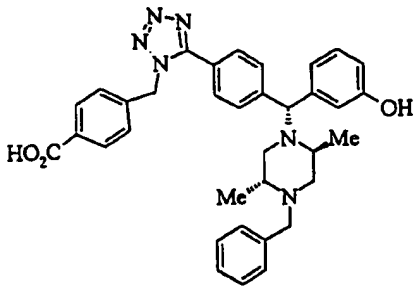
was prepared by reductive alkylation of the compound of Example 92 with benzaldehyde using a method similar to that described for Preparation 8.

Rf: 0.15 (4/5; ethyl acetate/pentane)

EXAMPLE 96

(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)-4-methylbenzoic acid.

The compound of the following formula:



was prepared by hydrolysis of the compound of Example 95 using a method similar to that described for Example 19.

m/z: 589 (MH^+)

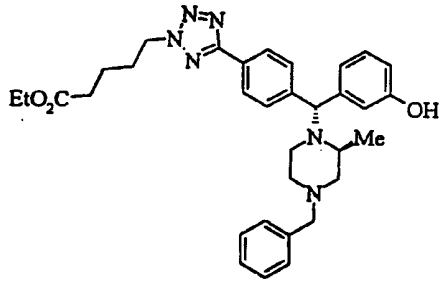
δ_H (300MHz, DMSO-d_6): 9.33 (1H, s), 7.93 (2H, m), 7.70-7.03 (12H, m), 6.65 (3H, m), 5.85 (2H, s), 5.00 (1H, br m), 3.80 (1H, m), 3.20 (1H,), 2.17-1.80 (6H, m), 1.08 (6H, m).

Found: C, 67.73; H, 6.23; N, 12.94. $C_{35}H_{36}N_6O_3.2.0H_2O$ requires C, 67.28; H, 6.45; N, 13.45%

EXAMPLE 97

Ethyl 5-(5-{4-[(R)-α-(2(S)-4-benzyl-2-methyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valerate.

The compound of the following formula:



was prepared using a method similar to that described for Example 42 using the compounds of Preparations 43, 44 and 66.

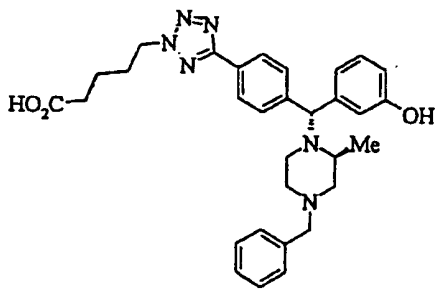
R_f: 0.4 (1/1; ethyl acetate/pentane)

δ_H (400MHz, $CDCl_3$): 8.02 (2H, d), 7.55 (2H, d), 7.30-7.20 (5H, m), 7.12 (1H, m), 6.88 (1H, m), 6.78 (1H, s), 6.63 (1H, m), 4.85 (1H, br s), 4.64 (2H, t), 4.12 (2H, q), 3.47 (2H, q), 2.87 (1H, br s), 2.65-2.30 (8H, m), 2.06 (2H, m), 1.69 (2H, m), 1.24 (3H, t), 1.11 (3H, d).

EXAMPLE 98

(+)-5-(5-{4-[(R)-α-(2(S)-4-benzyl-2-methyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valeric acid.

The compound of the following formula:



was prepared by hydrolysis of the compound of Example 97 using a method similar to that described for Example 19.

R_f: 0.25 (80/20/4; dichloromethane/methanol/ammonium hydroxide)

m/z: 542 (MH^+)

δ_H (400MHz, DMSO-d_6): 7.94 (2H, d), 7.56 (2H, d), 7.35-7.15 (5H, m), 7.05 (1H, dd), 6.80 (2H, m), 6.57 (1H, m), 4.64 (3H, m), 3.40 (2H, m), 2.84 (1H, m), 2.60-2.20 (6H, m), 1.91 (4H, m), 1.40 (2H, t), 1.02 (3H, d).

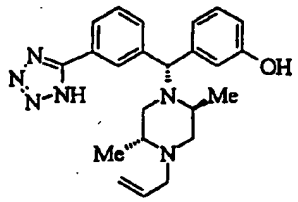
Found: C, 63.09; H, 6.58; N, 14.14. $C_{31}H_{36}N_6O_3.2.75H_2O$ requires C, 63.03; H, 7.09; N, 14.24%

$[\alpha]_D$ +31° (c=0.1, methanol)

EXAMPLE 99

(+)-3-{5-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-tetrazolyl}benzene

The compound of the following formula:



was prepared by desilylation of the compound of Preparation 33 using a method similar to that described for Example 55.

R_f: 0.23 (80/20/3; dichloromethane/methanol/ammonium hydroxide)

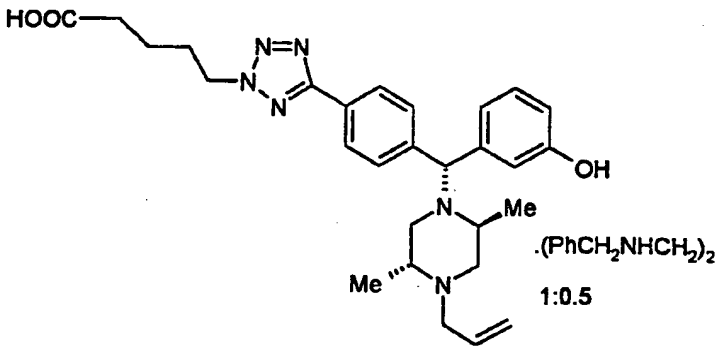
m/z: 405 (MH^+)

δ_H (400MHz, DMSO-d_6): 9.35 (1H, br s), 8.16 (1H, s), 7.82 (1H, m), 7.42 (1H, m), 7.13 (1H, t), 6.73 (2H, m), 6.66 (1H, m), 5.82 (1H, m), 5.25 (2H, m), 5.02 (1H, br s), 3.38-3.13 (4H, m), 2.93 (1H, m), 2.82 (1H, m), 2.68 (2H, m), 2.39 (1H, m), 2.0 (1H, m), 1.10 (3H, d), 1.04 (3H, d).

$[\alpha]_D$ +25.1° (c=0.11, methanol)

EXAMPLE 100

Preparation of the Benzathine Salt of compound of Example 42



N,N-Dibenzylethylenediamine (1.19g, 4.96mmol), the compound of Example 42 (5g, 9.91 mmol) and 5%v/v water in methyl ethyl ketone (12ml) were heated at reflux. The clear mixture was allowed to cool to room temperature, and stirred for 48 hours. The white crystalline suspension was filtered off and washed with cold solvent (3.1ml), and dried under vacuum at room temperature for 18 hours. Yield 3.46g (55%) of the salt as a white solid with a sharp melting point of 139°C.

HPLC analysis shows there to be 19.7% N,N dibenzylethylenediamine and 80% compound of Example 42 to be present by total area analysis. Water is present at 0.3%. This gives a stoichiometric ratio of compound to base of 1:0:5.

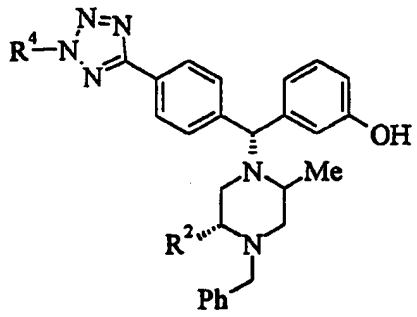
Molecular Formula $C_{36.3}H_{46.6}N_{7.0}O_{3.1}$

C,H,N Theoretical %C, 69.14; %H,7.45;%N,15.55.

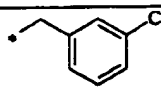
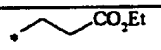
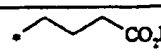
Actual %C,68.90; %H,7.92; %N,15.56.

EXAMPLE 101-103

The following compounds of the general formula:



were prepared by a similar method to that described for Preparation 5 using the corresponding aldehydes (Preparations 67, 69, and 70) and the corresponding piperazine derivatives (either Preparation 26 or Preparation 66).

Ex	R^2	R^4	Data
101	Me		R_f: 0.42 (dichloromethane/methanol; 95:5) *m/z*: 603 (MH^+) δ_H (300MHz, $CDCl_3$): 8.12 (1H, s), 8.03 (3H, m), 7.57 (3H, m), 7.48 (1H, t), 7.22 (6H, m), 6.78 (1H, d), 6.68 (2H, m), 5.82 (2H, s), 5.08 (2H, br s), 3.90 (4H, m), 3.20 (1H, d), 2.73 (1H, m), 2.60 (3H, m), 2.02 (2H, m), 1.08 (6H, m).
102	H		R_f: 0.12 (ethyl acetate/pentane; 1:2) δ_H (300MHz, $CDCl_3$): 8.02 (1H, s), 7.57 (2H, d), 7.25 (5H, m), 7.15 (1H, t), 6.88 (1H, d), 6.80 (1H, s), 6.63 (1H, m), 4.93 (2H, t), 4.85 (1H, s), 3.47 (2H, m), 3.10 (2H, t), 2.88 (1H, m), 2.65-2.30 (6H, m), 1.22 (3H, t), 1.12 (3H, d).
103	H		R_f: 0.28 (ethyl acetate/pentane; 1:2) δ_H (300MHz, $CDCl_3$): 8.02 (1H, s), 7.58 (2H, d), 7.32-7.10 (6H, m), 6.90 (1H, d), 6.81 (1H, m), 6.63 (1H, m), 4.85 (1H, s), 4.72 (2H, t), 3.68 (3H, s), 3.56-3.40 (2H, m), 2.88 (1H, m), 2.65-2.30 (6H, m), 1.12 (3H, d).

Example 101: Methyl (5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)-3-methylbenzoate.

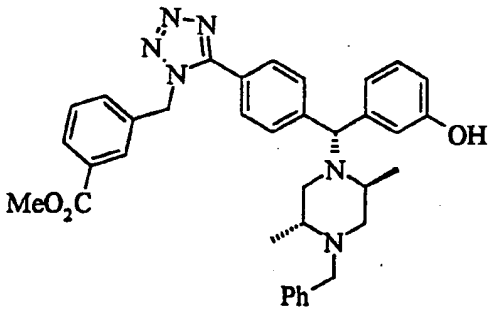
Example 102: Ethyl 3-(5-{4-[(R)-α-(2(S)-4-benzyl-2-methyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)propionate.

Example 103: Methyl 4-(5-{4-[(R)-α-(2(S)-4-benzyl-2-methyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)butanoate.

EXAMPLE 104

Methyl (5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)-3-methylbenzoate.

The compound of the following formula:



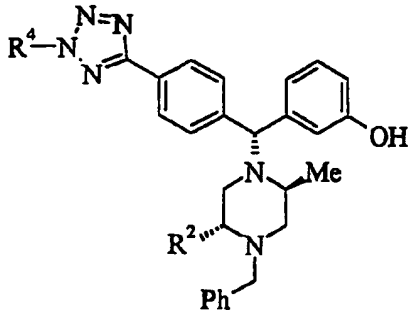
was prepared using a similar method to that described for Preparation 5 using the compounds of Preparations 26, 44 and 68.

R_f: 0.31 (dichloromethane/methanol/ammonium hydroxide; 95/5/0.5)

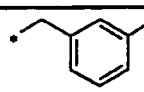
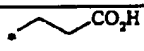
m/z: 603 (MH^+)

EXAMPLE 105-107

The following compounds of the general formula:



were prepared by hydrolysis of the corresponding esters using a method similar to that described for Example 19.

Ex	R^2	R^4	Data
105	Me		R_f: 0.22 (dichloromethane/methanol/ammonium hydroxide; 80/20/3) *m/z*: 589 (MH^+) δ_H (300MHz, d_6-DMSO): 8.00-7.84 (4H, m), 7.59-7.40 (4H, m), 7.30-7.08 (6H, m), 6.70 (3H, m), 6.03 (3H, m), 4.97 (1H, s), 3.75 (1h, d), 3.25 (1H, d), 2.60 (4H, m), 1.97 (2H, m), 1.02 (6H, m). Found: C, 67.88; H, 5.89; N, 13.57. $C_{35}H_{36}N_6O_3.3/2H_2O$ requires C, 68.27; H, 6.38; N, 13.65%
106	H		R_f: 0.05 (ethyl acetate/methanol/triethylamine; 78.5/20/15) *m/z*: 513 (MH^+) δ_H (300MHz, d_6-DMSO): 9.29 (1H, s), 7.95 (2H, d), 7.58 (2H, d), 7.32-7.19 (5H, m), 7.07 (1H, t), 6.88-6.79 (2H, m), 6.59 (1H, d), 4.88 (2H, t), 4.75 (1H, s), 3.55-3.21 (2H, m), 3.05 (2H, t), 2.88 (2H, t), 2.60-2.20 (6H, m), 1.03 (3H, t).
107	H		R_f: 0.25 (dichloromethane/methanol/ammonium hydroxide; 80/20/4) *m/z*: 527 (MH^+) δ_H (300MHz, d_6-DMSO): 7.97 (2H, d), 7.58 (2H, d), 7.25-7.18 (5H, m), 7.05 (1H, m), 6.83-6.78 (2H, m), 6.58 (1H, d), 4.76-4.63 (2H, m), 3.52-3.20 (2H, m), 2.87 (1H, m), 2.60-1.98 (8H, m), 1.03 (3H, d). Found: C, 64.15; H, 6.45; N, 14.92. $C_{30}H_{34}N_6O_3.2H_2O$ requires C, 64.02; H, 6.81; N, 14.94%

Example 105: (5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)-4-methylbenzoic acid.

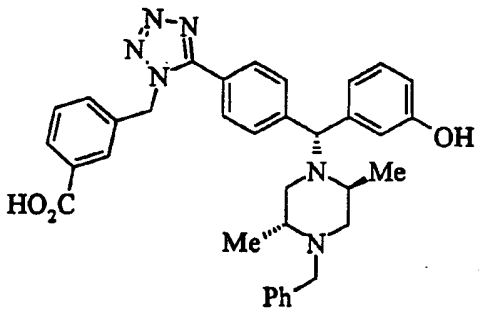
Example 106: 3-(5-{4-[(R)-α-(2(S)-4-benzyl-2-methyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)propionic acid.

Example 107: 4-(5-{4-[(R)-α-(2(S)-4-benzyl-2-methyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)butanoic acid.

EXAMPLE 108

(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)-3-methylbenzoic acid.

The compound of the following formula:



was prepared using a similar method to that described for Example 19 using the compound of Example 104.

R_f: 0.23 (dichloromethane/methanol/ammonium hydroxide; 95/5/0.5)

m/z: 589 (MH^+)

δ_H (300MHz, d_6-DMSO): 7.83 (1H, d), 7.68 (3H, d), 7.55 (2H, d), 7.41 (1H, t), 7.35-7.09 (1H, m), 6.68 (3H, m), 5.88 (2H, s), 5.00 (1H, s), 3.77 (1H, d), 3.25 (1H, d), 2.60 (4H, m), 2.00 (1H, m), 1.88 (1H, m), 1.03 (6H, m).

Found: C, 69.21; H, 6.04; N, 13.84. $C_{35}H_{36}N_6O_3.H_2O$ requires C, 69.29; H, 6.31; N, 13.85%

EXAMPLE 109

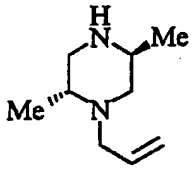
The delta opioid agonist activity of a number of compounds were determined in mouse vas deferens (as described above) with the following results:

Example	pIC_{50}
1	9.7
4	10.9
42	9.5

PREPARATIONS

PREPARATION 1

(-)-(2R,5S)-1-allyl-2,5-dimethylpiperazine



Trans-2,5-dimethylpiperazine (600g), slurried in toluene (1200ml), was heated to 85°C with stirring, at which temperature, the solid dissolved completely. The solution was allowed to cool to room temperature gradually, with stirring, allowing slow precipitation of the solid, then cooled to 10°C using an ice bath. The solid was filtered, washed with fresh, cold toluene (250mls), and dried under vacuum (50°C) overnight to yield a yellow crystalline solid (518.5g).

Recrystallised trans-2,5-dimethylpiperazine (259.5g) was slurried in cyclohexane (2.59 l) at room temperature. Sodium hydroxide solution (5M; 500ml) was added in one go with tetrabutylammonium chloride (4.3g) and the reaction mixture was stirred whilst the allyl bromide solution (302.4g) in cyclohexane (300ml) was added in a stream, over approximately 30 mins. The temperature of the reaction mixture rose slowly to 33°C over 30 mins, and was stirred for a further 1 hr. T.l.c analysis showed that the organic phase contained mostly mono-allylated product, with traces of bis-allylated impurity and starting material. The aqueous contained mostly starting material and some mono-allylated product. The two phases were separated and the aqueous was stirred with fresh cyclohexane (2.5L). Allyl bromide (82.5g) in cyclohexane (100ml), and sodium hydroxide solution (5M, 136ml) were added, and the mixture was stirred at room temperature for 1 hr. The phases were separated and the two cyclohexane phases were combined. The cyclohexane phase was backwashed with NaOH (1M, 200ml) to remove traces of starting material and this wash was added to the aqueous layer and kept on one side. The organic extracts (containing only mono- and bis- allylated material) were stirred with H_2O (1.5L), and the pH of the mixture adjusted to precisely 8.0 using c.HCl. TLC showed the aqueous contained mono with a faint trace of bis. Organic contained bis with a faint trace of mono. The layers were separated, and the pH of the aqueous adjusted to 13.5 using NaOH (10M), and extracted with CH_2Cl_2 (4x1L). The previously held-back aqueous washings were extracted with CH_2Cl_2 (4x1L). The combined organic

extracts were dried over $MgSO_4$ and stripped (50°C) to yield racemic 1-allyl-2,5-dimethylpiperazine as a yellow, mobile oil (278.9 g, 80%). [R_f = 0.4, (CH_2Cl_2/MeOH/NH_3; 80:20:1)]

A solution of racemic 1-allyl-2,5-dimethylpiperazine (537.7g) in acetone (1075 ml) was added in one portion to a stirred solution of (1R,3S)-(+)-camphoric acid in acetone (5.2L) at 40°C. Stirring was continued at 40°C and a white precipitate began to form after approximately five minutes, which soon became very thick. The reaction mixture was stirred at gentle reflux for a further 1 hr before being cooled to 10°C in an ice bath, and filtered. The precipitate was slurry-washed with fresh acetone (2L), then washed on the filter pad with more acetone (1L). The camphoric acid salt of (+)-(2S,5R)-1-allyl-2,5-dimethylpiperazine was dried under vacuum (60°C) overnight to yield a white solid (577g).

The crude enriched (-)-(2R,5S)-1-allyl-2,5-dimethylpiperazine (185.5g) was redissolved in acetone (370ml) and added to a solution of di-p-tolyl-D-tartaric acid monohydrate (486.5g) in acetone (6.8L) at 40°C. The reaction mixture was gently refluxed for 1hr. The reaction mixture was cooled to 10°C in an ice bath, filtered, washed with fresh acetone (3x500mls), and dried under vacuum (60°C) overnight to afford the tartrate salt as a white solid (466.4g, mpt 191.7°C). The di-p-tolyl-D-tartrate salt (466.4g) was fully dissolved in methanol (10L) at gentle reflux. The resulting pale yellow solution was distilled at atmospheric pressure to approximately half its original volume. The resulting clear solution was allowed to cool to room temperature and stirred for 72 hrs, during which time a thick white precipitate formed. The precipitate was filtered, washed with fresh methanol (2x500mls) and dried under vacuum (50°C) overnight to yield a white solid (382.1 g, mpt 194.3°C).

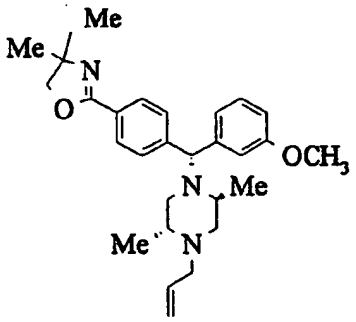
A solution of sodium hydroxide (2M, 3l) and dichloromethane (3l) were stirred together at room temperature. The di-p-tolyl-D-tartrate salt from above (371.4g) was added in one go, and the mixture stirred for 1 hr. The phases were separated and the aqueous washed with fresh CH_2Cl_2 (3x1L). The organic extracts were combined and evaporate in vacuo to afford the title compound (-)-(2R,5S)-1-allyl-2,5-dimethylpiperazine as a mobile yellow oil (104.3g,).

Rf: 0.30 (93/7/1; dichloromethane/methanol/ammonium hydroxide)

$[\alpha]_D$ -54.8° (c=1.19, Ethanol)

PREPARATION 2

2-4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]phenyl-4,4-dimethyl-4,5-dihydro-1,3-oxazole

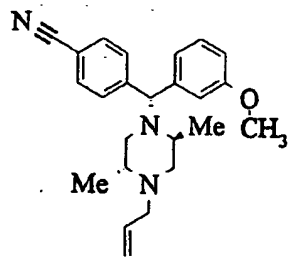


A solution of the Compound of Preparation 1 (1.5g), benzotriazole (1.16g) and 4-[(4,4-dimethyl)-1,3-oxazolin-2-yl]benzaldehyde (1.98g) (Preparation 45) in toluene (25ml) was heated under reflux with azeotropic removal of water for 3.5 hours. The solution was cooled to ambient temperature and added to a cold solution (-10°C) of 3-methoxyphenylmagnesium bromide (prepared from 3.64g of the corresponding bromide and 0.475g of magnesium turnings) in tetrahydrofuran (40ml) at such a rate as to maintain the internal temperature in the range -10 to 0°C. The resulting solution was stirred at 0°C for 15 minutes, ambient temperature for 30 minutes and then quenched with 2N hydrochloric acid solution. The layers were separated and the aqueous solution extracted with diethyl ether (2x). The combined organic extracts were discarded. The aqueous solution was basified to pH 9 and extracted with diethyl ether (3x). The combined extracts were washed successively with water, 2N sodium hydroxide, water and brine. The organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (30% Et_2O/CH_2Cl_2 + 1% MeOH) to afford the title compound. The αS-diastereomer was also isolated.

m/z: 476 (MH^+)

PREPARATION 3

4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]benzonitrile



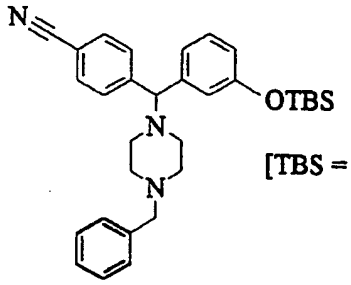
Phosphorus oxychloride (4.04ml) was added dropwise to a stirred solution of the compound of Preparation 2 (4.93g) in dry pyridine (30ml). The dark brown solution was stirred at 85-95°C for 18 hours, cooled in an ice-bath and quenched with excess 2N sodium hydroxide solution. Extraction with dichloromethane followed by drying (sodium sulphate) and evaporation in vacuo gave a brown semi-solid. The residue was purified by flash chromatography over silica gel (20% diethyl ether in dichloromethane) to afford the title compound, 3.21g.

m/z: 376 (MH+)

Rf: 0.42 (70/30/0.1 dichloromethane/diethyl ether/methanol)

PREPARATION 4

(a) **(±)-4-cyano-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-*tert*-butyldimethylsilyloxybenzyl]benzene.**



[TBS = t-butyldimethylsilyl]

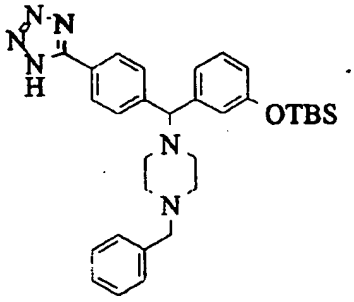
A solution of (±)1-benzylpiperazine (8.8g), benzotriazole (5.95g) and 4-cyanobenzaldehyde (6.55g) in toluene (150ml) was heated under reflux with azeotropic removal of water for 30 minutes. The solution was cooled to ambient temperature and added to a cold solution (-25°C) of 3-tert-butyldimethylsilyloxyphenylmagnesium bromide (prepared from 28.7g of the corresponding bromide and 2.43g of magnesium

turnings) in tetrahydrofuran (100ml) at such a rate as to maintain the internal temperature in the range -20°C. The resulting solution was stirred at 0°C for 15 minutes, ambient temperature for 30 minutes and then quenched with saturated aqueous ammonium chloride solution. The layers were separated and the aqueous solution extracted with diethyl ether (2x 200ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (5-20% ethyl acetate/hexane) to afford the title compound, 17.0g.

m/z: 498 (MH^+)

δ_H (400MHz, $CDCl_3$): 7.72 (2H, d), 7.56 (2H, d), 7.32-7.10 (6H, m), 6.95 (1H, d), 6.86 (1H, s), 6.66 (1H, d), 4.40 (1H, s), 3.44 (2H, s), 2.46-2.20 (8H, m), 0.90 (9H, s), 0.14 (6H, s).

(b) **(±)-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyl)oxybenzyl]phenyltetrazole**



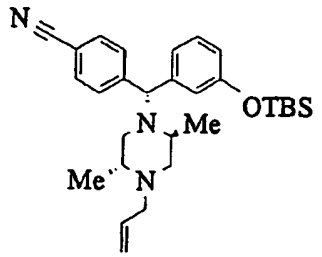
A solution of the first compound of part (a) (8.5g), dibutyltin oxide (1.05mg) and trimethylsilyl azide (4.3g) in dry toluene (50ml) were heated together under a gentle reflux for 5 hours. The reaction mixture was evaporated to dryness *in vacuo* and the residue purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide) to afford the title compound, 8.06 g.

m/z: 541 (MH^+)

δ_H (400MHz, $CDCl_3$): 7.90 (2H, d), 7.48 (2H, d), 7.34-7.20 (5H, m), 7.14 (1H, t), 7.00 (1H, d), 6.94 (1H, s), 6.68 (1H, d), 4.32 (1H, s), 3.56 (2H, s), 2.50-2.28 (8H, m), 0.90 (9H, s), 0.16 (6H, s).

PREPARATION 5

(+)-4-cyano-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-*tert*-butyldimethylsilyloxybenzyl]benzene.



A solution of (-)-(2R,5S)-1-allyl-2,5-dimethylpiperazine (21.6g), benzotriazole (16.68g) and 4-cyanobenzaldehyde (18.35g) in toluene (800ml) was heated under reflux with azeotropic removal of water for 3 hours. The solution was cooled to ambient temperature and added to a cold solution (-10°C) of 3-*tert*-butyldimethylsilyloxyphenylmagnesium bromide (prepared from 79g of the corresponding bromide and 6.8g of magnesium turnings) in tetrahydrofuran (500ml) at such a rate as to maintain the internal temperature in the range -10 to 0°C. The resulting solution was stirred at 0°C for 15 minutes, ambient temperature for 30 minutes and then quenched with saturated aqueous ammonium chloride solution. The layers were separated and the aqueous solution extracted with diethyl ether (2x 200ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (5-20% ethyl acetate/dichloromethane) to afford the title compound, 4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-*tert*-butyldimethylsilyloxybenzyl]cyanobenzene, 32.9g.

m/z: 476 (MH^+)

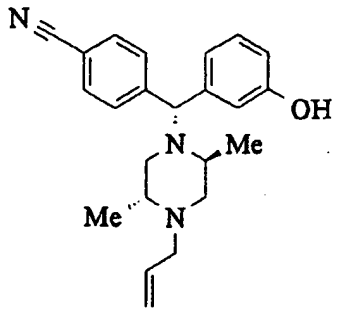
R_f: 0.35 (90/10/2; hexane/ethyl acetate/diethylamine)

Found: C, 72.26; H, 8.78; N, 8.09. $C_{29}H_{41}N_3OSi.3/10EtOAc$ requires C, 72.23; H, 8.71; N, 8.37%

$[\alpha]_d$ +22.9° (c=0.112, methanol)

PREPARATION 6

4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzonitrile



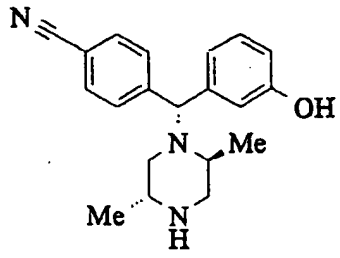
A solution of the compound of Preparation 5 (4.75g) and tetraethylammonium fluoride (3.70g) in tetrahydrofuran (100ml) was stirred at room temperature for 4 hours. The mixture was partitioned between ethyl acetate and water, the layers separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried (MgSO4) and evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel using gradient elution (hexane to ethyl acetate) to afford the title compound, 3.46g.

m/z: 362 (MH+)

R_f: 0.21 (1/1 hexane/ethyl acetate)

PREPARATION 7

4-[(*R*)-1-[(2*S*,5*R*)-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzonitrile



Tris(triphenylphosphine)rhodium(I) chloride (1.0g) was added to a solution of the compound of Preparation 6 (3.37g) in acetonitrile (80ml) and water (20ml). The reaction mixture was heated under a gentle reflux and the solvent allowed to distil off slowly. Additional acetonitrile/water (100ml; 4:1 v/v) was added a such a rate as to maintain a steady distillation. After the addition of solvent was complete the distillation was continued until the volume was reduced to approximately 50ml. The cooled

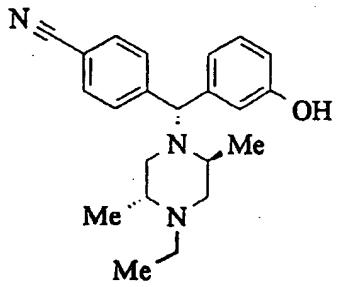
solution evaporated to dryness *in vacuo* and the residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide;) to afford the title compound, 2.48g.

m/z: 322 (MH+)

R_f 0.20 (93/7/1 dichloromethane/methanol/ammonia)

PREPARATION 8

4-[(*R*)-1-[(2*S*,5*R*)-4-ethyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzonitrile



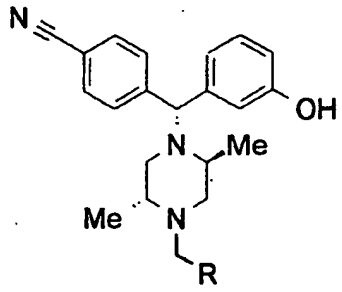
To a solution of the compound of Preparation 7 (482mg) and acetaldehyde (132mg) in tetrahydrofuran (10ml) containing glacial acetic acid (100mg) was added sodium triacetoxyborohydride (636mg). The mixture was stirred at room temperature for 1 hour and then poured into ethyl acetate and washed with saturated sodium hydrogen carbonate solution and saturated brine. The organic phase was dried (MgSO4) and evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel using gradient elution (100% dichloromethane to 6% methanol/dichloromethane) to afford the title compound as a white foam, 295mg.

m/z: 350 (MH+)

Rf: 0.32 (93/7/1 dichloromethane/methanol/ammonia)

PREPARATIONS 9 to 13

The following compounds of the general formula:



or salts thereof, were prepared from the compound of Preparation 7 by reductive alkylation with the appropriate aldehyde by similar methods to that used in Preparation 8.

Prep	R	Yield	*m/z*	Rf Solvent
9	Et	460mg	364	0.35 (93/7/1)
10	Ph	541mg	412	0.57 (93/7/1)
11	Thiazol-2-yl	546mg	419	0.44 (93/7/1)
12	H	407mg	336	0.30 (93/7/1)
13	CO_2H	467mg	380	0.77 (77/20/3)

solvent system dichloromethane/methanol/ammonia

Preparation 9 [(*R*)-1-[(2*S*,5*R*)-4-propyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzonitrile

Preparation 10 [(*R*)-1-[(2*S*,5*R*)-4-benzyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzonitrile

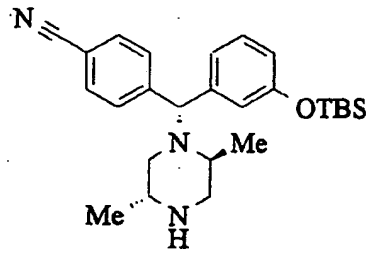
Preparation 11 [(*R*)-1-[(2*S*,5*R*)-2,5-dimethyl-4-(1,3-thiazol-2-ylmethyl)-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzonitrile

Preparation 12 [(*R*)-1-[(2*S*,5*R*)-2,4,5-trimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzonitrile

Preparation 13 (2*R*,5*S*)-4-[(*R*)-1-(4-cyanophenyl)-1-(3-hydroxyphenyl)methyl]-2,5-dimethyl-1-piperazinylacetic acid

PREPARATION 14

4-[(*R*)-1-[(2*S*,5*R*)-2,5-dimethyl-1-piperazinyl]-1-(3-(*tert*-butyldimethylsilyloxy)phenyl)methyl]benzonitrile



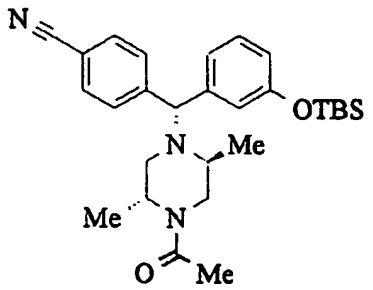
Tris(triphenylphosphine)rhodium(I) chloride (0.77g) was added to a solution of the compound of Preparation 5 (10g) in acetonitrile (80ml) and water (20ml). The reaction mixture was heated under a gentle reflux and the solvent allowed to distil off slowly. Additional acetonitrile/water (100ml; 4:1 v/v) was added a such a rate as to maintain a steady distillation. After the addition of solvent was complete the distillation was continued until the volume was reduced to approximately 50ml. The cooled solution was partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The layers were separated and the organic phase was dried (MgSO4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (90/10/2 dichloromethane/methanol/ammonium hydroxide;) to afford the title compound, 8.60g.

m/z: 436 (MH+)

Rf: 0.31 (93/7/1 dichloromethane/methanol/ammonia)

PREPARATION 15

4-[(*R*)-1-[(2*S*,5*R*)-4-acetyl-2,5-dimethyl-1-piperazinyl]-1-(3-(*tert*-butyldimethylsilyl)oxyphenyl)methyl]benzonitrile



A solution of the compound of Preparation 14 (870mg), triethylamine (303mg) and acetic anhydride (224mg) in dichloromethane (15ml) was stirred at room temperature for 2 hours. The reaction mixture was poured into water and extracted with

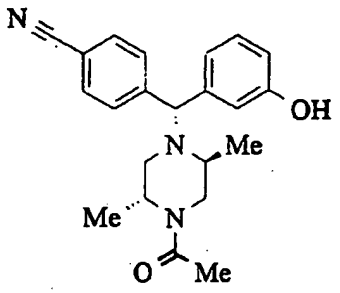
dichloromethane (3x 50ml). The combined extracts were dried (MgSO4) and evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel (ethyl acetate) to give the title compound, 781mg.

m/z: 478 (MH+)

Rf: 0.43 (ethyl acetate)

PREPARATION 16

4-[(*R*)-1-[(2*S*,5*R*)-4-acetyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzonitrile



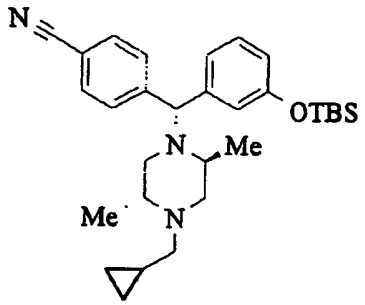
To a solution of the compound of Preparation 15 (775mg) in tetrahydrofuran (19ml) was added a solution of tetraethylammonium fluoride (600mg) in water (1ml) and the resulting mixture was stirred at room temperature for 22 hours. The mixture was partitioned between ethyl acetate and water and the layers separated. The organic extracts were washed with water and saturated brine solution, dried (MgSO4) and evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel (ethyl acetate) to afford the title compound, 616mg.

m/z: 364 (MH+)

Rf: 0.27 (ethyl acetate)

PREPARATION 17

4-[(*R*)-1-[(2*S*,5*R*)-4-cyclopropylmethyl-2,5-dimethyl-1-piperazinyl]-1-(3-(*tert*-butyldimethylsilyloxy)phenyl)methyl]benzonitrile



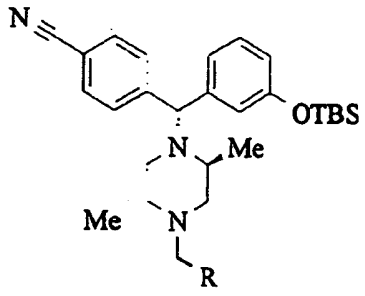
To a solution of the compound of Preparation 14 (870mg) and cyclopropane carboxaldehyde (168mg) in tetrahydrofuran (20ml) containing glacial acetic acid (132mg) was added sodium triacetoxyborohydride (848mg). The mixture was stirred at room temperature for 1.5 hours and then poured into ethyl acetate and washed with saturated sodium hydrogen carbonate solution and saturated brine. The organic phase was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (100% hexane to 50% hexane/ethyl acetate) to afford the title compound as a gum, 798mg.

m/z: 490 (MH+)

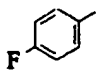
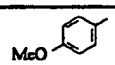
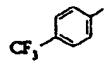
Rf: 0.57 (ethyl acetate)

PREPARATIONS 18 to 20

The following compounds of the general formula:



or salts thereof, were prepared from the compound of Preparation 14 by reductive alkylation with the appropriate aldehyde by similar methods to that used in Preparation 17.

Prep. No.	R	Yield	*m/z*	Rf (1:1 EtOAc/Hexane)
18		76%	544	0.81
19		87%	556	0.73
20		85%	594	0.81

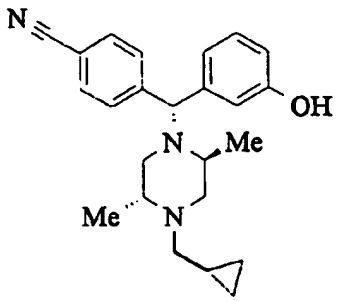
Preparation 18 [(*R*)-1-[(2*S*,5*R*)-4-(4-fluorobenzyl)-2,5-dimethyl-1-piperazinyl]-1-(3-(*tert*-butyldimethylsilyl)oxyphenyl)methyl]benzonitrile.

Preparation 19 [(*R*)-1-[(2*S*,5*R*)-4-(4-methoxybenzyl)-2,5-dimethyl-1-piperazinyl]-1-(3-(*tert*-butyldimethylsilyl)oxyphenyl)methyl]benzonitrile.

Preparation 20 [(*R*)-1-[(2*S*,5*R*)-4-(4-trifluoromethylbenzyl)-2,5-dimethyl-1-piperazinyl]-1-(3-(*tert*-butyldimethylsilyl)oxyphenyl)methyl] benzonitrile.

PREPARATION 21

4-[(*R*)-1-[(2*S*,5*R*)-4-cyclopropylmethyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzonitrile



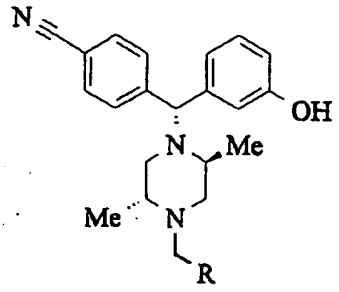
To a solution of the compound of Preparation 17 (786mg) in tetrahydrofuran (18ml) was added a solution of tetraethylammonium fluoride (592mg) in water (2ml) and the resulting mixture was stirred at room temperature for 20 hours. The mixture was partitioned between ethyl acetate and water and the layers separated. The organic extracts were washed with water and saturated brine solution, dried (MgSO4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (ethyl acetate) to afford the title compound, 617mg.

m/z: 376 (MH+)

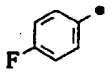
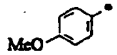
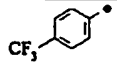
Rf: 0.35 (ethyl acetate)

PREPARATIONS 22 to 24

The following compounds of the general formula:



or salts thereof, were prepared by desilylation of the corresponding silyl ethers (see Preparations 18 to 20) by similar methods to that used in Preparation 21.

Prep. No.	R	Yield	*m/z*	Rf (1:1 EtOAc/Hexane)
22		99%	430	0.5
23		81%	442	0.37
24		90%	480	0.60

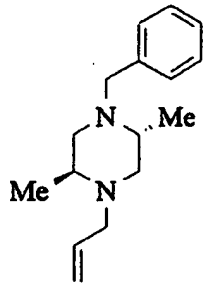
Preparation 22 [(*R*)-1-(2*S*,5*R*)-2,5-dimethyl-4-[4-fluorobenzyl]-1-piperazinyl-1-(3-hydroxyphenyl)methyl]benzonitrile.

Preparation 23 [(*R*)-1-(2*S*,5*R*)-2,5-dimethyl-4-[4-methoxybenzyl]-1-piperazinyl-1-(3-hydroxyphenyl)methyl]benzonitrile.

Preparation 24 [(*R*)-1-(2*S*,5*R*)-2,5-dimethyl-4-[4-(trifluoromethyl)benzyl]-1-piperazinyl-1-(3-hydroxyphenyl)methyl]benzonitrile.

PREPARATION 25

(2*S*,5*R*)-1-allyl-4-benzyl-2,5-dimethylpiperazine



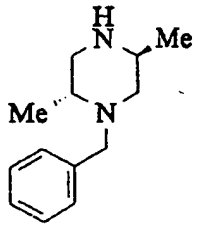
To a suspension of the camphoric acid salt of (+)-(2S,5R)-1-allyl-2,5-dimethylpiperazine from Preparation 1 (78.2g) and benzaldehyde (26.5g) in tetrahydrofuran (500ml) containing glacial acetic acid (2ml) was added sodium triacetoxyborohydride (93.3g) portionwise over 10 minutes. The resulting mixture was stirred at room temperature for 4 hours. The reaction was partitioned between ethyl acetate (1500ml) and aqueous sodium hydroxide (750ml of 2N solution). The layers were separated and the organic phase was washed with 10% sodium metabisulphite solution (200ml) and saturated brine solution. The organic layer was dried (MgSO4) and evaporated to dryness in vacuo to give the title compound, 52.1g.

m/z: 245 (MH+)

Rf: 0.63 (93/7/1 dichloromethane/methanol/ammonium hydroxide)

PREPARATION 26

(-)-(2R,5S)-1-benzyl-2,5-dimethylpiperazine



Tris(triphenylphosphine)rhodium(I) chloride (3g) was added to a solution of the compound of Preparation 25 (52.1g) in acetonitrile (400ml) and water (80ml). The reaction mixture was heated under a gentle reflux and the solvent allowed to distil off slowly. Additional acetonitrile/water (250ml; 4:1 v/v) was added a such a rate as to maintain a steady distillation. After the addition of solvent was complete the distillation was continued until the volume was reduced to approximately 200ml. The cooled

solution was partitioned between ethyl acetate and 2N hydrochloric acid. The layers were separated and the organic phase extracted with further 0.5N hydrochloric acid. The combined aqueous extracts were basified with 2N sodium hydroxide solution and extracted into dichloromethane. The combined organic extracts were dried (MgSO4) and evaporated to dryness *in vacuo*, to afford the title compound, 38.2g.

m/z: 205 (MH^+)

Rf: 0.27 (93/7/1 dichloromethane/methanol/ammonia)

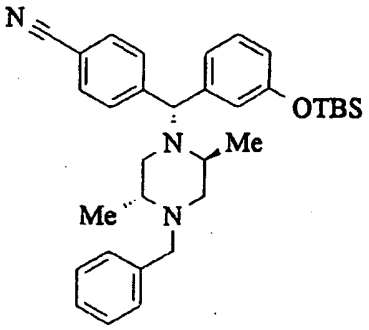
$[\alpha]_D$ -113°(c 0.2, methanol)

PREPARATION 27

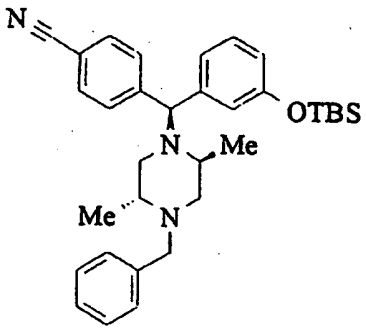
[(*R*)-1-(2*S*,5*R*)-2,5-dimethyl-4-benzyl-1-piperazinyl-1-(3-(*tert*-butyldimethylsilyl)oxyphenyl)methyl]benzonitrile.

and

[(*S*)-1-(2*S*,5*R*)-2,5-dimethyl-4-benzyl-1-piperazinyl-1-(3-(*tert*-butyldimethylsilyl)oxyphenyl)methyl]benzonitrile.



and



A solution of the compound of Preparation 26 (10.2g), benzotriazole (5.95g) and 4-cyanobenzaldehyde (6.55g) in toluene (150ml) was heated under reflux with azeotropic removal of water for 3 hours. The solution was cooled to ambient temperature and added to a cold solution (-25°C) of 3-*tert*-butyldimethylsilyloxyphenylmagnesium bromide (prepared from 28.7g of the corresponding bromide and 2.4g of magnesium turnings) in tetrahydrofuran (100ml) at such a rate as to maintain the internal temperature at -25°C. The resulting solution was stirred at 0°C for 15 minutes, ambient temperature for 30 minutes and then quenched with 2N sodium hydroxide solution. The layers were separated and the aqueous solution extracted with ethyl acetate (2x). The combined organic extracts were washed with water, and brine. The organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (100% dichloromethane to

10% ethyl acetate/dichloromethane) to afford the title compounds. The αR-diastereomer was the first to elute, 17.38g.

m/z: 526 (MH+)

Rf: 0.62 (3/1 hexane/ethyl acetate)

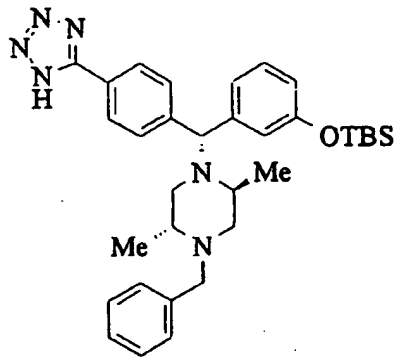
The αS-diastereomer was also isolated and eluted second, 2.61g.

m/z: 526 (MH+)

Rf: 0.53 (3/1 hexane/ethyl acetate)

PREPARATION 28

[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-(*tert*-butyldimethylsilyl)oxybenzyl]phenyltetrazole



A solution of the first compound of Preparation 27 (7.88g) dibutyltin oxide (750mg) and trimethylsilyl azide (3.45g) in dry toluene (50ml) were heated together under a gentle reflux for 5.5 hours. The reaction mixture was evaporated to dryness *in vacuo* and the residue purified by column chromatography over silica gel (85/15/2 dichloromethane/methanol/ammonium hydroxide) to afford the title compound, 7.45g.

m/z: 569 (MH^+)

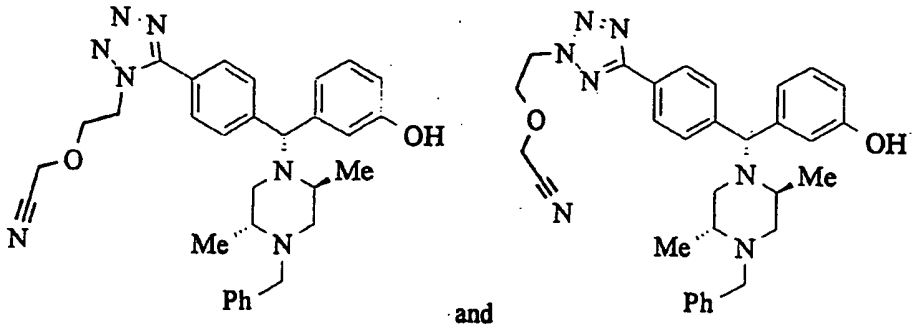
R_f: 0.44 (80/20/3 dichloromethane/methanol/ammonia)

PREPARATIONS 29 AND 30

2-[2-(5-4-[(*R*)-1-[(2*S*,5*R*)-4-benzyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]phenyl-2*H*-1,2,3,4-tetrazol-2-yl)ethoxy]acetonitrile

and

2-[2-(5-4-[(*S*)-1-[(2*S*,5*R*)-4-benzyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]phenyl-2*H*-1,2,3,4-tetrazol-1-yl)ethoxy]acetonitrile



and

A solution of the compound of Preparation 28 (2.12g), 5-bromo-3-oxopentanenitrile (620mg)) and potassium carbonate (1.38g) in acetonitrile (40ml)) was heated under a gentle reflux for 2.5 hours. The cooled reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was separated and extracted with further ethyl acetate. The combined organic extracts were washed with water, saturated brine solution, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was dissolved in tetrahydrofuran (20ml) and tetraethylammonium fluoride (1.48g) in water (2ml) added. The mixture was stirred at room temperature for 20 hours then partitioned between ethyl acetate and water. The layers were separated and the organic phase was washed with water and saturated brine solution, dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (100% hexane to 60% ethyl acetate/hexane) to afford the N-2 isomer, 1.43g, followed by the N-1 isomer, 137mg,.

Data for N-2 Isomer:

m/z: 538 (MH+)

Rf: 0.26 (1/1 ethyl acetate/hexane)

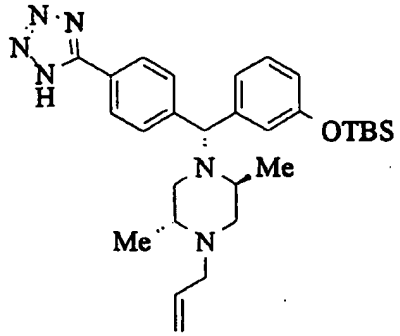
Data for N-1 Isomer:

m/z: 538 (MH+)

Rf: 0.16 (1/1 ethyl acetate/hexane)

PREPARATION 31

4-{5-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-*tert*-butyldimethylsilyloxybenzyl]-tetrazolyl}benzene



A solution of the compound of Preparation 5 (8.1g), dibutyltin oxide (3.0g) and trimethylsilyl azide (9.96g) in dry toluene (60ml) was heated at 80°C for 72 hours under nitrogen. To the cooled reaction mixture was added 880 ammonium hydroxide solution and the layer separated. The aqueous solution was diluted with water (100ml) and extracted with ethyl acetate (2X100ml). The combined organic extracts were washed with water and saturated brine, dried (Na2SO4) and evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel using gradient elution (90/10/2 to 80/20/3 dichloromethane/methanol/ammonia) to afford the title compound, 7.76g.

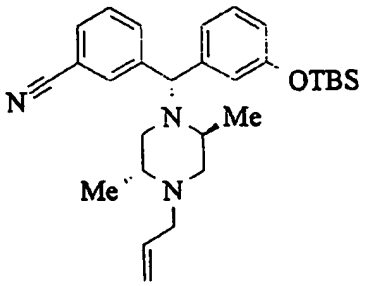
m/z: 519 (MH^+)

R_f: 0.40 (80/20/3 dichloromethane/methanol/ammonia)

PREPARATION 32

3-cyano-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-*tert*-butyldimethylsilyloxybenzyl]benzene.

The compound of the following formula:



was prepared by a similar method to that used in Preparation 5 but using 3-cyanobenzaldehyde.

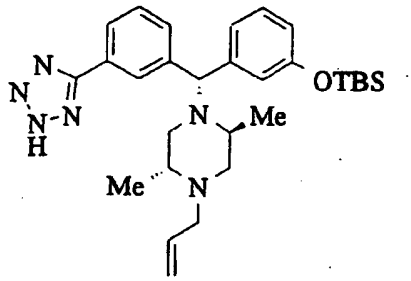
m/z: 476 (MH+)

Rf: 0.35 (90/10/2; hexane/isopropanol/ammonium hydroxide)

Found: C, 72.68; H,8.71; N, 8.28. $C_{29}H_{41}N_3OSi$ requires C, 73.21; H, 8.69; N, 8.83%

PREPARATION 33

(+)-3-{5-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-*tert*-butyldimethylsilyloxybenzyl]-tetrazolyl}benzene



A mixture of the compound of Preparation 32 (5g), azidotrimethylsilane (2.67g) and dibutyltin oxide (0.94g) in toluene (40ml) was heated, with stirring, at 70°C for 72 hours. The cooled reaction mixture was poured into ammonium hydroxide and ethyl acetate and the layers separated. The ammonium hydroxide solution was diluted with water and extracted with further ethyl acetate (2x). The combined organic extracts were washed with saturated brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel (dichloromethane/methanol/ammonium hydroxide; 80/20/3) to afford the title compound, 4.91g.

m/z: 519 (MH+)

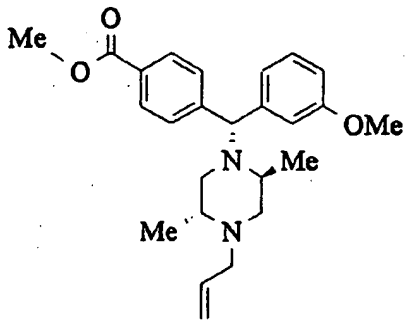
Rf: 0.25 (80/20/3; ethyl acetate/methanol/ammonium hydroxide)

$[\alpha]_D$ +22.6° (c=0.124, methanol)

Found: C, 64.71; H,8.16; N, 15.70. $C_{29}H_{42}N_6OSi.H_2O$ requires C, 64.89; H, 8.26; N, 15.66%

PREPARATION 34

(+)-Methyl 4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]benzoate



A solution of the compound of Preparation 1 (11.55g), benzotriazole (8.93g) and methyl 4-formylbenzoate (12.32g) in toluene (100ml) was heated under reflux with azeotropic removal of water for 3 hours. The solution was cooled and added to a cold solution (-20°C) of 3-methoxyphenylmagnesium bromide (prepared from 28.05g of the 3-bromoanisole and 3.65g of magnesium turnings) in tetrahydrofuran (100ml) at such a rate as to maintain the internal temperature in the range -20 to -15°C. The resulting solution was stirred at -20°C for 5 minutes and then warmed to room temperature, quenched with saturated aqueous ammonium chloride solution (200ml). The layers were separated and the aqueous solution extracted with ethyl acetate (2x 200ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (Hexane to 50% ethyl acetate/hexane) to afford the title compound, 27.95g.

m/z: 409 (MH^+)

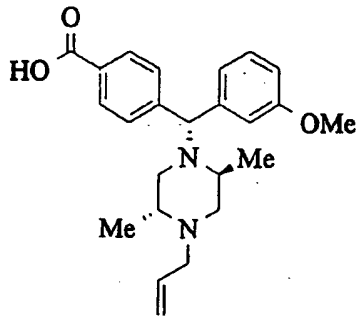
Rf: 0.31 (95/5/0.5; hexane/isopropanol/ammonium hydroxide)

$[\alpha]_d$ +20.7° (c=0.145, methanol)

Found: C, 71.12; H, 7.66; N, 6.58. $C_{25}H_{32}N_2O_3.1/5H_2O$ requires C, 71.13; H, 6.67; N, 6.58%

PREPARATION 35

(+)-4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]benzoic acid



To a solution of the compound from Preparation 34 (27.9g) in methanol (200ml) was added 2N aqueous sodium hydroxide solution. The resulting suspension was stirred at room temperature for 20 hours, and then at 50°C for 2 hours. Solid sodium hydroxide (3.2g) was added and the mixture warmed at 50°C for a further hour. The cooled solution was evaporated to dryness and the residue purified by column chromatography over silica gel (dichloromethane/methanol/ammonium hydroxide; 77/20/3) to afford the title compound, 11.06g

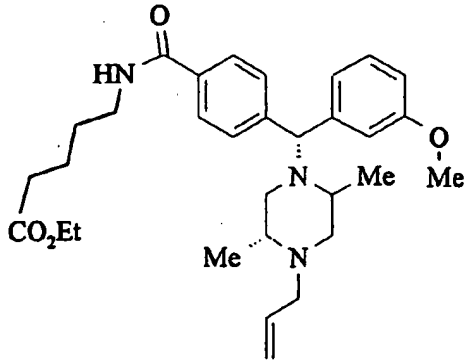
δ_H (300MHz, $CDCl_3$): 7.97 (2H, d), 7.52 (2H, d), 7.23 (1H, m), 6.79 (3H, m), 6.60 (1H, v br s), 5.91 (1H, m), 5.23 (3H, m), 3.77 (3H, s), 3.41 (1H, dd), 3.02 (1H, dd), 2.90 (1H, m), 2.80 (1H, m), 2.64 (2H, m), 2.28 (1H, m), 2.05 (1H, m), 1.19 (3H, d), 1.05 (3H, d).

m/z: 395 (MH^+)

$[\alpha]_D$ +17.1° c=0.105, methanol.

PREPARATION 36

Ethyl 5-(4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]phenylcarboxamido)pentanoate



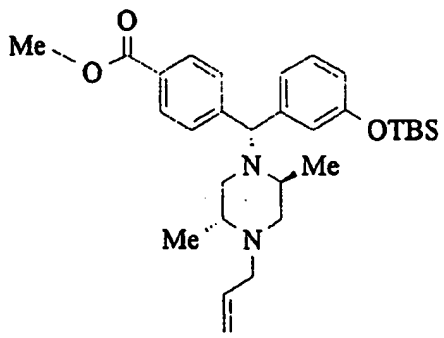
A solution of the compound of Preparation 35 (2.512g), 1-hydroxybenzotriazole (1.55g), diisopropylethylamine (2.44ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.464g) in dry dichloromethane (30ml) was stirred under nitrogen for 1 hour. To this was added ethyl 5-aminovalerate.HCl (1.39g) and further dichloromethane (10ml). The reaction mixture was stirred at room temperature overnight, diluted with dichloromethane (100ml) and washed with water (20ml). The organic solution was dried (sodium sulphate) and evaporated in vacuo. The brown residue was purified by column chromatography over silica gel (98/2; dichloromethane/methanol) to afford the title compound, 2.965g.

m/z: 522 (MN+)

Rf: 0.31 (95/5; dichloromethane/methanol)

PREPARATION 37

Methyl 4-[(R)-1-[(2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-tert-butyldimethylsilyloxyphenyl)methyl]benzoate



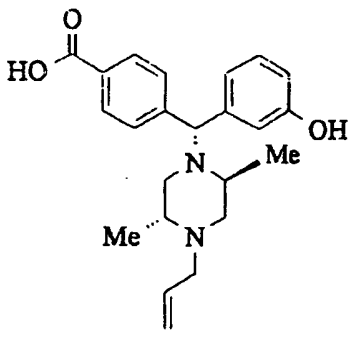
A solution of (-)-(2R,5S)-1-allyl-2,5-dimethylpiperazine (22.26g), benzotriazole (17.18g) and methyl 4-formylbenzoate (23.7g) in toluene (400ml) was heated under reflux with azeotropic removal of water for 3 hours. The solution was cooled and added to a cold solution (-20°C) of 3-*tert*-butyldimethylsilyloxyphenylmagnesium bromide (prepared from 82.9g of corresponding bromide and 7.29g of magnesium turnings) in tetrahydrofuran (300ml) at such a rate as to maintain the internal temperature in the range -20 to -15°C. The resulting solution was stirred at -20°C for 1.5 hours and then warmed to room temperature, quenched with saturated aqueous ammonium chloride solution (200ml). The layers were separated and the aqueous solution extracted with ethyl acetate (2x 200ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (85/15/2 hexane/ethyl acetate/diethyl amine) to afford the title compound, 54.45g.

m/z: 509 (MH^+)

R_f: 0.44 (93/7/1 dichloromethane/methanol/ammonium hydroxide)

PREPARATION 38

(+)-4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]benzoic acid



To a solution of the compound of Preparation 37 (54.45g) in methanol (150ml) and dioxane (100ml) was added sodium hydroxide (214ml of 5N aqueous solution), The resulting solution was stirred at room temperature for 18 hours, cooled to 0°C and neutralised to pH 7-8 with hydrochloric acid. The solution was evaporated to dryness in vacuo and the residue purified by column chromatography over silica using gradient elution (95/5/0.5 to 80/20/3 dichloromethane/methanol/ ammonium hydroxide) to afford the title compound, 25.98g.

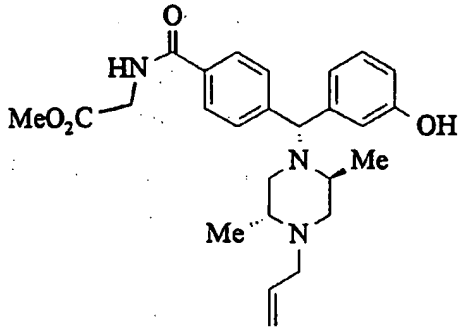
m/z: 381 (MH+)

Rf: 0.14 (80/20/3 dichloromethane/methanol/ ammonium hydroxide)

$[\alpha]_D$ +25.4° (c 0.12, methanol)

PREPARATION 39

(+)-Methyl 2-(4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]phenylcarboxamido)acetate



A solution of the compound of Preparation 38 (11.3g), 1-hydroxybenzotriazole (7.22g), diisopropylethylamine(21.4ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.83g) and glycine methyl ester hydrochloride (4.48g) in dry dichloromethane (150ml) was stirred at room temperature for 48 hours. The solution was washed with water and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (93/2/0.5 ethyl acetate/methanol/ammonia) to give the title compound, 12.8g.

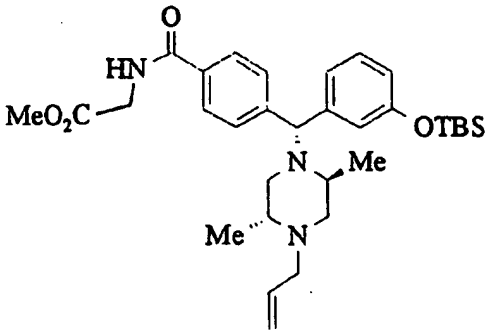
m/z: 452 (MH+)

Rf: 0.4 (95/5/0.5 ethyl acetate/methanol/ammonia)

$[\alpha]_D$ +20.8° (c 0.13, methanol)

PREPARATION 40

Methyl 2-(4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-*tert*-butyldimethylsilyloxyphenyl)methyl]phenylcarboxamido)acetate



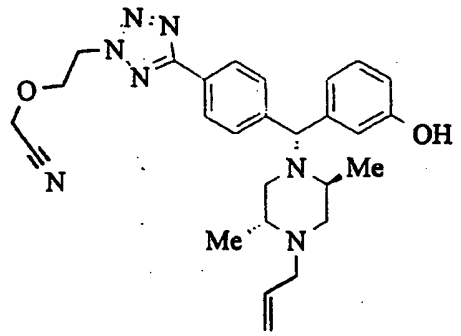
A solution of the compound of Preparation 39 (10g), imidazole (1.58g) and chloro*tert*-butyldimethylsilane (3.5g) in dichloromethane (60ml) was stirred under nitrogen for 18 hours. The reaction mixture was diluted with dichloromethane (100ml) and washed successively with water (50ml) and saturated aqueous sodium hydrogen carbonate (50ml), dried over sodium sulphate and evaporated *in vacuo* to afford the title compound, 12.29g.

m/z: 566 (MH+)

Rf: 0.62 (95/5/0.5 dichloromethane/methanol/ammonia)

PREPARATION 41

2-[2-(5-4-[(*R*)-1-[(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl]-1-(3-hydroxyphenyl)methyl]phenyl-2*H*-1,2,3,4-tetrazol-2-yl)ethoxy]acetonitrile



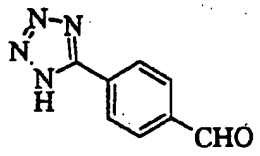
A solution of the compound of Preparation 31 (5.34g), 2-bromoethoxyacetonitrile (1.47g) and potassium carbonate (3.88g) in 2-butanone (60ml) was heated under a gentle reflux for 18 hours. The cooled reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was separated and extracted with further ethyl acetate. The combined organic extracts were washed with water, saturated brine solution, dried (Na2SO4) and evaporated to dryness in vacuo to give a brown gum. The residue was purified by column chromatography over silica gel (95/5/0.5 diethyl ether/ethanol /ammonia) to afford the title compound, 3.46g.

m/z: 488 (MH^+)

R_f: 0.61 (95/5/0.5 diethyl ether/ethanol/ammonium hydroxide)

PREPARATION 42

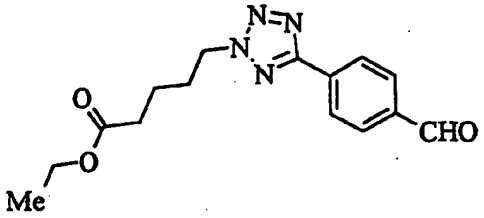
4-(1*H*-1,2,3,4-tetraazol-5-yl)benzaldehyde



Trimethylsilyl azide (25g) and dibutyltin oxide (8.8g) were added to a solution of 4-cyanobenzaldehyde (13g) in toluene (200ml). The reaction was stirred with warming to 50°C over 1hr, and then warmed to 96°C over 30 minutes and maintained at that temperature for 3 hours. The solvent was evaporated *in vacuo* to afford an orange oil which was purified by column chromatography over silica gel (ethyl acetate). The crude product was dissolved in refluxing toluene and allowed to cool with stirring overnight. The resulting slurry was granulated in an ice-bath for 1 hour, filtered and washed with cold toluene. The filtrate was evaporated in vacuo to afford a solid. The solid was dissolved in refluxing ethyl acetate (250ml) and concentrated to 60ml by rotary evaporation. The solution was cooled to room temperature and then granulated in an ice bath. The thick slurry was collected by filtration, washed and dried, with warming, in a vacuum oven to afford the title compound, 12g.

PREPARATION 43

Ethyl 5-[5-(4-formylphenyl)-2*H*-1,2,3,4-tetraazol-2-yl]pentanoate



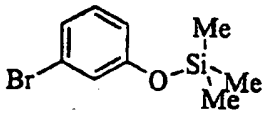
A mixture of the compound of Preparation 42 (450g), potassium carbonate (715.5g) and ethyl 5-bromovalerate (593.1g) in acetonitrile (4500ml) was heated together under reflux for 5 hours. The suspension was cooled to room temperature and water (4500ml) added. The aqueous portion was separated and extracted with ethyl acetate (4500ml). The combined organic portions were washed with water (2000ml) and evaporated to dryness *in vacuo* to afford the title compound as a damp pale orange solid, 928g.

m/z: 303 (MH+)

δ_H (300MHz, $CDCl_3$): 10.1 (1H, s), 8.32 (2H, d), 8.05 (2H, d), 4.70 (2H, t), 4.1 (2H, q), 2.40 (2H, t), 2.15 (2H, m), 1.72 (2H, m), 1.22 (3H, t)

PREPARATION 44

3-Bromo-(trimethylsilyloxy)benzene

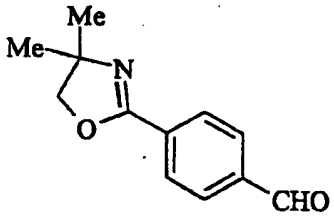


To a stirred solution of 3-bromophenol (382.3g) in acetonitrile (1725ml) under nitrogen was added hexamethyldisilazane (235.6g) over 20 minutes. Chlorotrimethylsilane was added dropwise to the clear solution over 20 minutes with stirring and the resulting white suspension was stirred at room temperature overnight. The slurry was removed by filtration and was washed with acetonitrile (200ml). The filtrate was evaporated in vacuo to a pale yellow oil which was distilled under vacuum (72°C at 0.5mmHg) to give the title compound, 541g, as a colourless oil.

δ_H (300MHz, $CDCl_3$): 7.10 (2H, m), 7.04 (1H, m), 6.80 (1H, m), 0.3 (9H, s)

PREPARATION 45

4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)- benzaldehyde



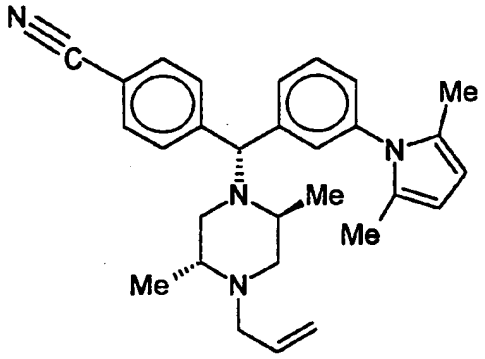
n-Butyl lithium (9.44ml, 2.5N solution in hexanes) was added to a solution of 2-(4-bromophenyl)-4,5-dihydro-4,4-dimethyl-oxazole [A.I. Meyers et al., J.O.C., 1974, 39, 2787] (5g) in tetrahydrofuran (80ml) at -78°C. The reddish solution was stirred at -78°C for 15 minutes before dimethylformamide (2.3g) was added dropwise. The resulting deep red solution was allowed to warm to room temperature, quenched with ammonium chloride solution and extracted into ether. The combined extracts were washed with brine, dried (sodium sulphate) and evaporated to dryness in vacuo. The residue was purified by column chromatography (30% ethyl acetate/hexane) to afford the title compound as a colourless liquid, 3.01g.

m/z: 204 (MH+)

δ_H (300MHz, $CDCl_3$): 10.04 (1H, s), 8.10 (2H, d), 7.88 (2H, d), 4.12 (2H, s), 1.38 (6H, s).

PREPARATION 46

4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(2,5-dimethylpyrrol-1-yl)benzyl]benzonitrile



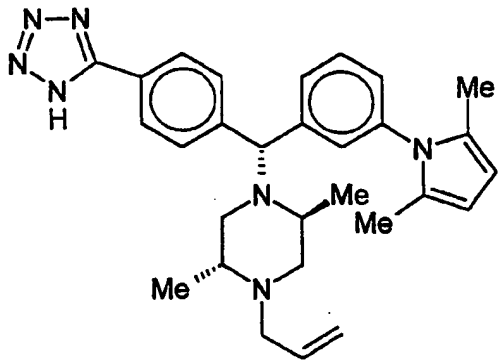
The title compound was prepared in a similar manner to Preparation 5 using the same starting materials except that the 3-(2,5-dimethylpyrrol-1-yl)phenylmagnesium bromide was used.

m/z : 439 (MH^+)

δ_H(300 MHz, d_6-DMSO) : 7.76 (2H,d), 7.58 (2H,d), 7.50 (1H,t), 7.32 (1H,d), 7.18 (1H,d), 7.02 (1H, d), 5.84-5.70 (3H, m), 5.32 (1H, s), 5.14 (1H, d), 5.08 (1H, d), 3.30 (1H, s), 3.18 (1H, m), 2.84 (1H, dd), 2.66 (1H, d), 2.60-2.42 (2H, m), 2.10 (1H, dd), 1.92 (6H,s), 1.72 (1H, m), 1.10 (3H,d), 0.92 (3H, d).

PREPARATION 47

4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-(2,5-dimethylpyrrol-1-yl)benzyl]phenyltetrazole



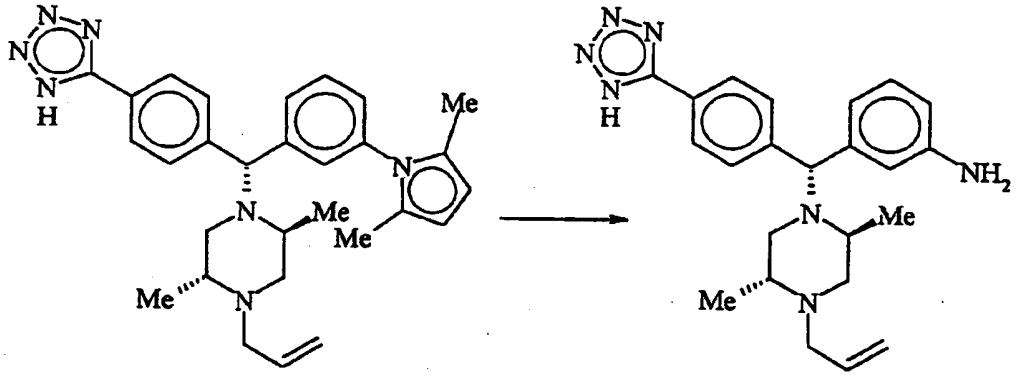
The title compound was prepared in a similar manner to the method of Example 52 using the compound of Preparation 46.

m/z : 482 (MH^+)

δ_H (300 MHz, d_6-DMSO) : 7.94 (2H, d), 7.60-7.44 (3H, m), 7.40 (1H,d), 7.20 (1H, d), 7.08 (1H,s), 5.82 (1H,m), 5.76 (2H, s), 5.36-5.18 (3H, m), 3.36 (1H, dd), 3.10 (1H, m), 2.90 (1H, d), 2.80 (1H, m), 2.72 (1H, d), 2.62 (1H, d), 2.36 (1H, m), 2.00-1.90 (8H, m), 1.18 (3H, d), 1.02 (3H, d).

PREPARATION 48

4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-aminobenzyl]phenyltetrazole



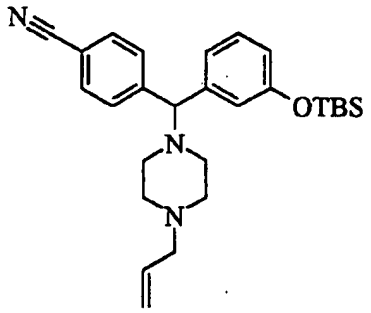
A mixture of the dimethylpyrrole starting material from Preparation 47, (170 mg; 0.00035 mole) and hydroxylamine hydrochloride (74 mgs; 0.00105 mole) in ethanol (3 ml) was heated at reflux for three days. The solvent was removed by rotary evaporation. The brown residue was then flash chromatographed on silica; eluant 90/10/1 → 85/15/2 → 80/20/3 CH_2Cl_2/MeOH/NH_4OH to give 54 mg (38%) of the desired product.

m/z: 404 (MH^+)

δ_H (300mhz, DMSO-d_6): 7.92 (2H,d); 7.50 (2H,d); 6.97 (1H,t), 6.45 (3H,m); 5.80 (1H,m); 5.25 (2H,m); 4.92 (1H,bs); 2.55 → 3.50 (7H,m); 2.20 → 2.40 (2H,m); 1.95 (2H,m); 1.00 (6H,2xd).

PREPARATION 49

(±)-4-cyano-[(R,S)-α-(4-allyl-1-piperazinyl)-3-*tert*-butyldimethylsilyloxybenzyl]benzene



A solution of 1-allyl piperazine (12.9g), benzotriazole (11.9g) and 4-cyanobenzaldehyde (13.1g) in toluene (350ml) was heated under reflux with azeotropic removal of water for an hour. The solution was allowed to cool to room temperature, and then added to a cooled solution (-10°C) of 3-*tert*-butyldimethylsilyloxyphenylmagnesium bromide (prepared from 57.2g of the corresponding bromide and 4.86g of magnesium turnings) in tetrahydrofuran (350ml), at such a rate that the internal temperature did not exceed 0°C. The resulting solution was stirred at 0°C for 15 minutes, followed by 30 minutes at room temperature. Aqueous saturated ammonium chloride solution was then carefully added, the phases separated and the aqueous layer extracted with diethyl ether (2x500ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give a brown oil. The residue was purified by column chromatography over silica gel (95/5/0.25 hexane/isopropanol/ammonium hydroxide) to afford the title compound (40g).

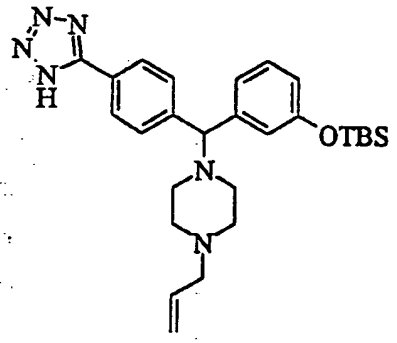
m/z: 447 (M^+)

R_f : 0.46 (90/10/0.75 hexane/isopropanol/ammonium hydroxide)

δ_H (400MHz, $CDCl_3$): 7.49-7.65 (4H, m), 7.12 (1H, dd), 6.82(1H, d), 6.84 (1H, s), 6.68 (1H, d), 5.84 (1H, m), 5.15 (2H, m), 4.20 (1H, s), 3.00 (2H, d), 2.44 (8H, m), 0.96 (9H, s), 0.15 (6H, s).

PREPARATION 50

(±)-[(R,S)-α-(4-allyl-1-piperazinyl)-3-*tert*-butyldimethylsilyl]oxybenzyl)phenyltetrazole



A solution of the compound of Preparation 49 (11g), dibutyl tin oxide (2.86g) and trimethylsilyl azide (9.22g) in toluene (100ml) were heated together under reflux for 48 hours. On cooling, the reaction mixture was partitioned between ammonium hydroxide solution and ethyl acetate. The phases were separated, and the aqueous layer, extracted with further ethyl acetate (2x200ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (90/10/2-85/15/2.5 dichloromethane/methanol/ammonium hydroxide) to afford the title compound.

m/z: 491 (MH^+)

R_f : 0.35 (80/20/3 dichloromethane/methanol/ammonium hydroxide)

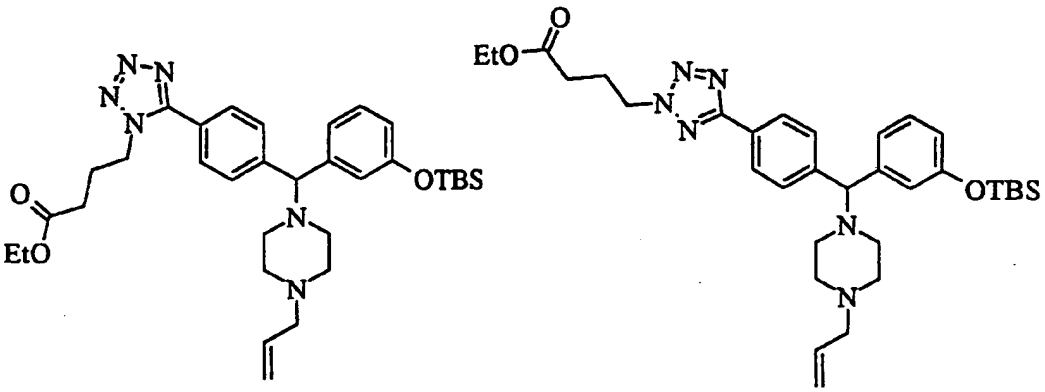
δ_H (400MHz, DMSO-d_6): 7.90 (2H, d), 7.50 (2H, d), 7.12 (1H, m), 6.87 (1H, d), 6.90 (1H, s), 6.63 (1H, d), 5.77 (1H, m), 5.20 (2H, m), 4.34 (1H, s), 3.16 (2H, d), 2.61 (4H, m), 2.36 (4H, m), 0.88 (9H, s), 0.11 (6H, s).

PREPARATION 51

(±)-Ethyl 4-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-*tert*-butyldimethylsilyloxybenzyl]phenyl}-1-tetrazolyl)butyrate

and

(±)-Ethyl 4-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-*tert*-butyldimethylsilyloxybenzyl]phenyl}-2-tetrazolyl)butyrate



A suspension of the compound of Preparation 50 (1g) and bis(tri-n-butyltin) oxide (596mg) in ethanol (5ml), was stirred under reflux for 2 hours. On cooling, the reaction mixture was evaporated to dryness *in vacuo* to afford a brown oil. This material was then heated under reflux in ethyl 4-bromobutyrate (16ml) for 90 minutes and on cooling the mixture was evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (50/50-100/0 ethyl acetate/hexane) to afford the N2 isomer, 550mg.

m/z: 605 (MH^+)

R_f : 0.19 (50/50 ethyl acetate/hexane)

δ_H (300MHz, DMSO-d_6): 7.95 (2H, d), 7.56 (2H, d), 7.14 (1H, dd), 6.99 (1H, d), 6.93 (1H, s), 6.64 (1H, d), 5.76 (1H, m), 5.10 (2H, m), 4.72 (2H, t), 4.32 (1H, s), 4.00 (2H, q), 2.92 (2H, d), 2.37 (10H, m), 2.19 (2H, m), 1.14 (3H, t), 0.88 (9H, s), 0.15 (6H, s).

and the N1 isomer, 200mg.

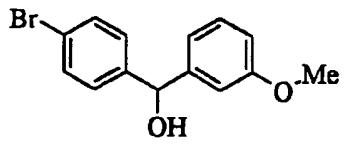
m/z: 605 (MH^+)

R_f : 0.06 (50/50 ethyl acetate/hexane)

δ_H (300MHz, DMSO-d_6): 7.72 (2H, d), 7.61 (2H, d), 7.16 (1H, dd), 7.00 (1H, d), 6.84 (1H, s), 6.66 (1H, d), 5.78 (1H, m), 5.12 (2H, m), 4.47 (2H, t), 4.38 (1H, s), 3.82 (2H, q), 2.93 (2H, d), 2.34 (10H, m), 2.03 (2H, m), 1.08 (3H, t), 0.90 (9H, s), 0.14 (6H, s).

PREPARATION 52

(±)-4-bromo-α-(3-methoxybenzene)benzyl alcohol



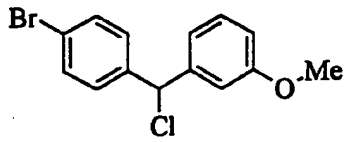
A solution of n-butyl lithium in tetrahydrofuran (10.8ml, 2.5M), was added dropwise to a cooled solution (-78°C) of 3-bromoanisole (50.5g) in tetrahydrofuran (200ml), and the resulting suspension stirred at -78°C under a nitrogen atmosphere for an hour. This suspension was then cannulated into a cooled solution (-78°C) of 4-bromobenzaldehyde (50g) in tetrahydrofuran (200ml) and the reaction maintained at this temperature for 3 hours. Saturated aqueous ammonium chloride solution was added and the mixture allowed to warm to room temperature. The layers were separated, and the aqueous phase extracted with diethyl ether. The combined organic extracts were washed with water, and evaporated to dryness *in vacuo*. The residue was suspended between diethyl ether (200ml) and saturated aqueous sodium metabisulphite solution (200ml) and the mixture filtered to remove the resulting white precipitate. The filtrate was separated and the organic layer dried ($MgSO_4$), and evaporated to dryness *in vacuo*, to give a yellow oil. This was triturated with pentane, to afford the title compound as a yellow crystalline solid, 42g.

m/z: 293 (MH^+)

δ_H (300MHz, $CDCl_3$): 7.46 (2H, d), 7.26 (3H, m), 6.90 (2H, m), 6.81 (1H, d), 5.76 (1H, s), 3.80 (3H, s), 2.25 (1H, s).

PREPARATION 53

(±)-4-bromo-α-(3-methoxybenzene)benzyl chloride

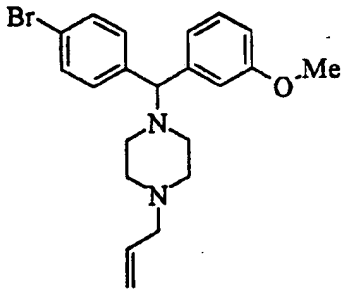


A solution of thionyl chloride (21ml) in dichloromethane (80ml) was added dropwise to an ice-cooled solution of the compound of Preparation 52 (42g) in dichloromethane (400ml), and the reaction stirred at room temperature for 90 minutes. The mixture was then evaporated to dryness *in vacuo*, and azeotroped with toluene, to afford the title compound as a brown solid, 45g.

δ_H (300MHz, $CDCl_3$): 7.48 (2H, d), 7.29 (3H, m), 6.95 (2H, m), 6.84 (1H, d), 6.03 (1H, s), 3.80 (3H, s).

PREPARATION 54

(±)-4-bromo-[(R,S)-α-(4-allyl-1-piperazinyl)-3-methoxybenzyl]benzene



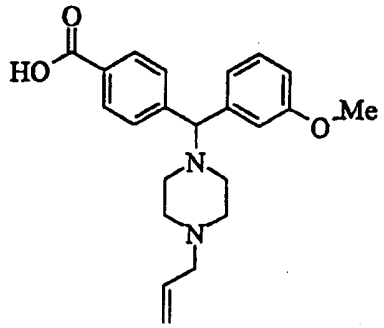
A suspension of 1-allyl piperazine (2.65g), the compound of preparation 53 (7.85g) and potassium carbonate (14.5g) in acetonitrile (50ml) was heated under a nitrogen atmosphere under reflux for 18 hours. On cooling, diethyl ether was added and the mixture filtered to remove residual solids. The filtrate was washed with water, then brine and the product extracted using 2N aqueous hydrochloric acid solution (4x25ml). This aqueous solution was then basified with 5N aqueous sodium hydroxide solution and extracted with diethyl ether (3x50ml). These combined organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give the title compound as a brown gum, 7.0g.

m/z: 401 (M^+)

δ_H (300MHz, $CDCl_3$): 7.38 (2H, d), 7.28 (2H, d), 7.16 (1H, dd), 6.94 (2H, m), 6.71 (1H, d), 5.85 (1H, m), 5.14 (2H, m), 4.17 (1H, s), 3.76 (3H, s), 3.00 (2H, d), 2.44 (8H, m).

PREPARATION 55

(±)-4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-methoxybenzyl]benzoic acid



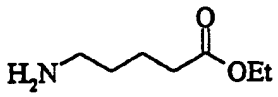
A solution of n-butyl lithium in tetrahydrofuran (1.15ml, 2.5M) was added dropwise to a cooled (-78°C) solution of the compound of Preparation 54 (968mg) in tetrahydrofuran (10ml), and the resulting orange solution stirred for 15 minutes. Carbon dioxide was bubbled through the reaction mixture and it was then allowed to warm to room temperature and stirring continued under a nitrogen atmosphere for 72 hours. 2N aqueous hydrochloric acid was added, and the resulting mixture basified with ammonium hydroxide solution and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel (80/20/3 dichloromethane/methanol/ammonium hydroxide) to afford the title compound as a white powder, 470mg.

m/z: 367 (MH^+)

δ_H (300MHz, $CDCl_3$): 7.88 (2H, d), 7.39 (2H, d), 7.09 (1H, dd), 6.88 (2H, m), 6.64 (1H, d), 5.90 (1H, m), 5.10 (3H, m), 4.20 (1H, s), 3.70 (3H, s), 3.00 (2H, d), 2.50 (4H, m), 2.40 (4H, m).

PREPARATION 56

Ethyl 5-aminovalerate hydrochloride



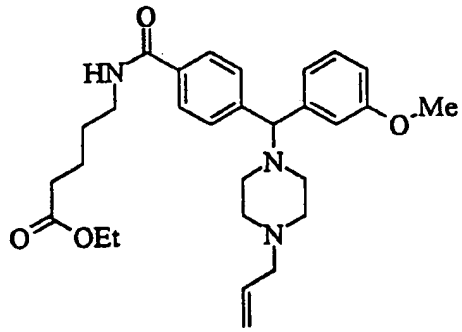
Hydrogen chloride gas was bubbled through a suspension of 5-aminovaleric acid (12g) in ethanol (100ml) and the reaction stirred under reflux for 90 minutes. On cooling, the mixture was evaporated to dryness *in vacuo*, to give an off-white solid. This material was recrystallised from ethanol/diethyl ether to afford the title compound, 15.1g.

m/z: 145 (M^+)

δ_H (300MHz, $CDCl_3$): 8.25 (2H, br.s), 4.12 (2H, t), 3.06 (2H, m), 2.36 (2H, t), 1.79 (4H, m), 1.23 (3H, t).

PREPARATION 57

(±)-Ethyl 5-{4-[(R,S)-(4-allyl-1-piperazinyl)-1-(3-methoxyphenyl)methyl]phenylcarboxamido}valerate



A solution of the compound of Preparation 55 (470mg), diisopropylamine (492µl), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (295mg), 1-hydroxybenzotriazole (312mg) and the compound of Preparation 56 (280mg) in dry dichloromethane (20ml), was stirred under a nitrogen atmosphere, at room temperature for 18 hours. Water (20ml) was added and the mixture extracted with dichloromethane (2x25ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel

(95/5/0.5 dichloromethane/methanol/ammonium hydroxide) to afford the title compound as an oil, 590mg.

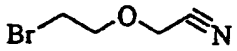
m/z: 494 (MH^+)

R_f: 0.47 (95/5/0.5 dichloromethane/methanol/ammonium hydroxide)

δ_H (300MHz, $CDCl_3$): 7.67 (2H, d), 7.50 (2H, d), 7.19 (1H, dd), 6.98 (2H, m), 6.72 (1H, d), 5.85 (1H, m), 5.16 (2H, m), 4.22 (1H, s), 4.13 (2H, q), 3.77 (3H, s), 3.44 (2H, m), 3.00 (2H, d), 2.48 (8H, m), 2.36 (2H, t), 1.67 (4H, m), 1.28 (3H, t).

PREPARATION 58

2-bromoethoxy acetonitrile



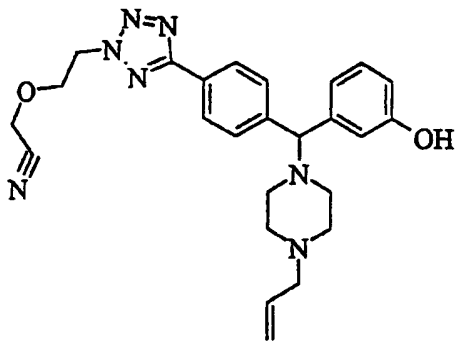
Triphenylphosphine (6.80g) was added portionwise to an ice-cooled solution of 2-hydroxyethoxyacetonitrile (*J.Org.Chem.* 20; 1990; 5337) (2.50g) and carbon tetrabromide (8.62g) in acetonitrile under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 hours and then evaporated to dryness *in vacuo*. The residue was triturated with a hexane/dichloromethane solution, the resulting mixture filtered and the filtrate evaporated to dryness *in vacuo* to give an oil. This material was purified by column chromatography over silica gel using gradient elution (66/34-50/50 hexane/dichloromethane) to afford the title compound as a colourless oil, 3.17g.

m/z: 163 (M^+)

δ_H (300MHz, $CDCl_3$): 4.35 (2H, s), 3.94 (2H, t), 3.51 (2H, t).

PREPARATION 59

(±)-2-(5-{4-[(R,S)-α-(4-allyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)ethoxy acetonitrile



A suspension of the compound of Example 55 (3.9g), the compound of Preparation 58 (1.26g) and potassium carbonate (3.3g) in 2-butanone (120ml) was heated under reflux for 72 hours. On cooling, water was added and the reaction mixture extracted with ethyl acetate (3x100ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (97/3-95/5 dichloromethane/methanol) and then again with (97/3/0-90/10/2 diethyl ether/ethanol/ammonium hydroxide) to afford the title compound, 1.74g.

m/z: 460 (MH^+)

R_f : 0.36 (95/5/0.5 diethyl ether/ethanol/ammonium hydroxide)

δ_H (400MHz, $CDCl_3$): 8.06 (2H, d), 7.54 (2H, d), 7.15 (1H, dd), 6.98 (1H, d), 6.91 (1H, s), 6.66 (1H, d), 5.88 (1H, m), 5.32 (1H, s), 5.17 (2H, m), 4.88 (2H, t), 4.22 (5H, m), 3.04 (2H, d), 2.51 (8H, m).

Found: C, 64.68; H, 6.33; N, 21.07. $C_{25}H_{29}N_5O_2.1/5H_2O$ requires C, 64.83; H, 6.40; N, 21.17%

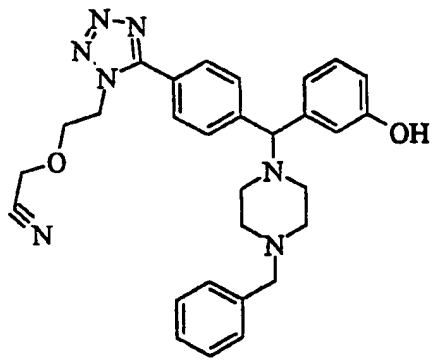
The N1 isomer was also isolated, 160mg.

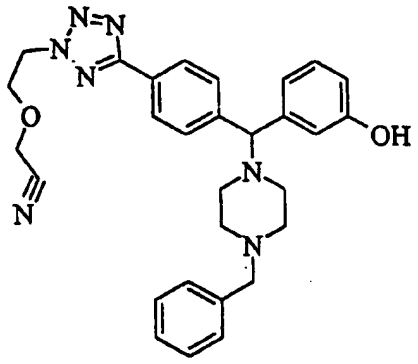
PREPARATION 60

2-(5-{4-(±)-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)ethoxyacetonitrile

and

2-(5-{4-(±)-[(R,S)-α-(4-benzyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)ethoxyacetonitrile





A suspension of the compound of Preparation 4b (2.16g), the compound of Preparation 58 (670mg) and potassium carbonate (1.66g) in acetonitrile (40ml), was stirred under reflux for 20 hours. On cooling, the reaction mixture was concentrated *in vacuo*, and the residue partitioned between ethyl acetate and water. The layers were separated and the aqueous solution extracted with ethyl acetate (2x50ml). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to give a brown oil. This material was then dissolved in tetrahydrofuran (20ml), tetraethylammonium fluoride (1.23g) added and the reaction stirred at room temperature for 18 hours. Water was added and the mixture extracted with ethyl acetate (3x30ml). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (75/25-65/35 hexane/ethyl acetate) and then again with (95/5 dichloromethane/methanol) to afford the N2 isomer, 1.55g

m/z: 510 (MH^+)

δ_H (400MHz, DMSO-d_6): 9.34 (1H, s), 7.98 (2H, d), 7.57 (2H, d), 7.26 (5H, m), 7.08 (1H, dd), 6.83 (2H, m), 6.56 (1H, d), 4.94 (2H, t), 4.48 (2H, s), 4.24 (1H, s), 4.10 (2H, t), 3.44 (2H, s), 2.22-2.48 (8H, m).

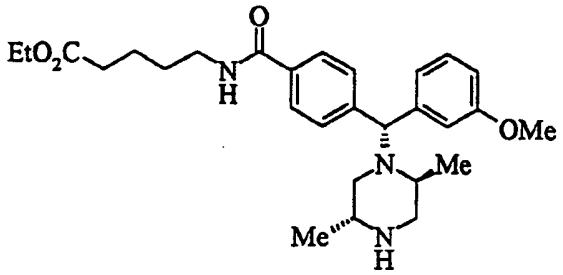
and the N1 isomer, 180mg.

m/z: 510 (MH^+)

δ_H (400MHz, DMSO-d_6): 9.36 (1H, s), 7.72 (2H, d), 7.61 (2H, d), 7.26 (5H, m), 7.08 (1H, dd), 6.83 (2H, m), 6.57 (1H, d), 4.65 (2H, t), 4.40 (2H, s), 4.30 (1H, s), 3.98 (2H, t), 3.47 (2H, s), 2.30-2.62 (8H, m).

PREPARATION 61

Ethyl 5-(4-[(*R*)-1-[(2*S*,5*R*)-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]phenylcarboxamido)valerate.



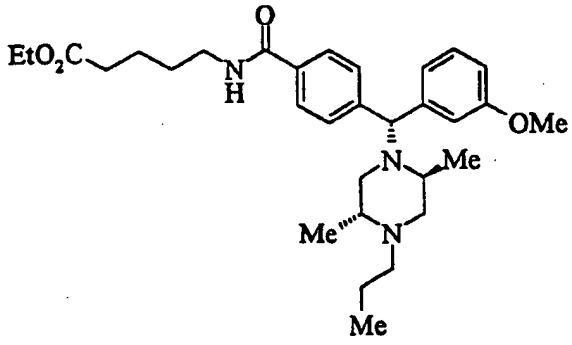
Tris(triphenylphosphine)rhodium(I) chloride (1.0g) was added to a solution of the compound of Preparation 36 (8.12g) in acetonitrile (160ml) and water (40ml). The reaction mixture was heated under a gentle reflux and the solvent allowed to distil off slowly. Additional acetonitrile/water (100ml; 4:1 v/v) was added at such a rate as to maintain a steady distillation. After the addition of solvent was complete the distillation was continued until the volume was reduced to approximately 60ml. The cooled solution was poured into ethyl acetate and washed with saturated aqueous sodium bicarbonate solution and saturated brine. The solution was dried (magnesium sulphate), evaporated to dryness *in vacuo* and the residue was purified by column chromatography over silica gel using gradient elution (100% dichloromethane to 60/40/1 dichloromethane/methanol/ammonium hydroxide) to afford the title compound, 6.35g.

m/z: 482 (MH^+)

R_f: 0.34 (93/7/1 dichloromethane/methanol/ammonium hydroxide)

PREPARATION 62

Ethyl 5-(4-[(*R*)-1-[(2*S*,5*R*)-4-propyl-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]phenylcarboxamido)pentanoate



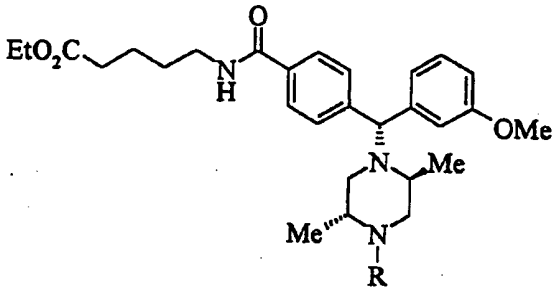
To a solution of the compound of Preparation 61 (600mg), propionaldehyde (102μg) and glacial acetic acid (100mg) in dry tetrahydrofuran (20ml) was added, with stirring, sodium triacetoxyborohydride (636mg). The resulting mixture was stirred at room temperature for 18 hours after which time it was poured into ethyl acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution, saturated brine, dried (magnesium sulphate) and evaporated to dryness in vacuo. The residue was purified by column chromatography over silica gel using gradient elution (100% dichloromethane to 95/5 dichloromethane/methanol) to afford the title compound, 611mg.

m/z: 524 (MH^+)

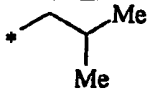
R_f: 0.62 (93/7/1 dichloromethane/methanol/ammonium hydroxide)

PREPARATION 63 to 65

The following compounds of the general formula:



were prepared from the compound of Preparation 61 by reductive alkylation with the appropriate aldehyde using a similar method to that described in Preparation 62.

Preparation number	R	R_f	*m/z* (MH+)
63		0.64	538
64		0.70	538
65		0.76	536

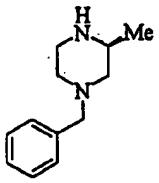
Preparation 63: Ethyl 5-(4-[(*R*)-1-[(2*S*,5*R*)-4-butyl-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]phenylcarboxamido)pentanoate

Preparation 64: Ethyl 5-(4-[(*R*)-1-[(2*S*,5*R*)-4-cyclopropylmethyl-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]phenylcarboxamido)pentanoate

Preparation 65: Ethyl 5-(4-[(*R*)-1-[(2*S*,5*R*)-4-*iso*-butyl-2,5-dimethyl-1-piperazinyl]-1-(3-methoxyphenyl)methyl]phenylcarboxamido)pentanoate

PREPARATION 66

(3S)-1-benzyl-3-methylpiperazine



(S)-(+)-2-Methylpiperazine (2.63g), benzylbromide (3.12ml) and potassium carbonate (5.4g) were heated together in acetonitrile (120ml) at 40°C for 3 days. The mixture was evaporated to dryness in vacuo and the residue partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The organic phase was separated, dried (magnesium sulphate) and evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using gradient elution (95/5/0 to 92/7/1 dichloromethane/methanol/ammonium hydroxide) to afford the title compound as a solid, 1.12g.

R_f: 0.25 (92/7/1; dichloromethane/methanol/ammonium hydroxide)

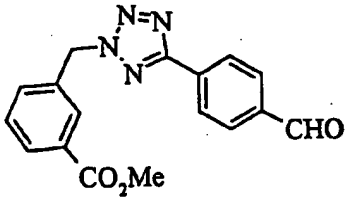
δ_H (300MHz, $CDCl_3$): 7.3 (5H, m), 3.5 (2H, s), 2.9 (3H, m), 2.77 (2H, m), 2.02 (1H, m), 1.65 (2H, m), 1.02 (3H, m).

PREPARATIONS 67 and 68

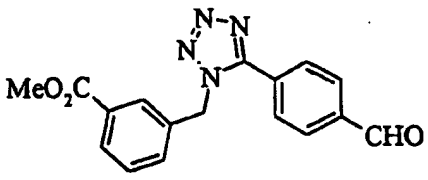
Methyl 3-[5-(4-formylphenyl)-2*H*-1,2,3,4-tetrazolyl-2-yl]methylbenzoate

and

Methyl 3-[5-(4-formylphenyl)-1*H*-1,2,3,4-tetrazolyl-2-yl]methylbenzoate



and



A mixture of the compound of Preparation 42 (3g), potassium carbonate (7.2g) and methyl 2-bromomethylbenzoate (4.35g) in dry acetonitrile (75ml) was heated together under reflux for 5 hours. The reaction mixture was cooled to room temperature and evaporated to dryness *in vacuo*. The residue was partitioned between water and ethyl acetate, and the organic layer separated, dried (sodium sulphate) and evaporated in vacuo. The residue was purified by column chromatography over silica gel using

gradient elution (80/20 to 50/50 hexane/ethyl acetate) to afford the title compounds. The N-2 isomer eluted first (2.92g)

m/z: 323 (MH^+)

mp: 113-114°C

δ_H (400MHz, $CDCl_3$): 10.08 (1H, s), 8.35 (2H, d), 8.15 (1H, s), 8.08 (1H, d), 8.00 (2H, d), 7.63 (1H, d), 7.49 (1H, t), 5.88 (2H, s), 3.95 (3H, s).

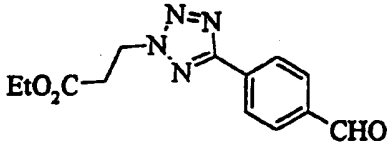
Found: C, 63.29; H, 4.33; N, 17.19. $C_{17}H_{14}N_4O_3$ requires C, 63.35; H, 4.38; N, 17.38% followed by the N-1 isomer (212mg)

m/z: 323 (MH^+)

δ_H (400MHz, $CDCl_3$): 10.12 (1H, s), 8.04 (3H, m), 7.83 (1H, s), 7.78 (2H, d), 7.47 (1H, t), 7.35 (1H, d), 5.71 (2H, s), 3.92 (3H, s).

PREPARATION 69

Ethyl 3-[5-(4-formylphenyl)-2*H*-1,2,3,4-tetrazolyl-2-yl]propionate



A mixture of the compound of Preparation 42 (3g), potassium carbonate (8.3g) and ethyl 3-bromopropionate (4.68g) in dry acetonitrile (70ml) was heated together at 50°C for 16 hours. The reaction mixture was cooled to room temperature and evaporated to dryness *in vacuo*. The residue was partitioned between water and ethyl acetate, and the organic layer separated, dried (sodium sulphate) and evaporated *in vacuo*. The crude residue containing both N-1 and N-2 isomers was purified by column chromatography over silica gel (1/2 pentane/ethyl acetate) to afford the title compound as a colourless oil, 1g.

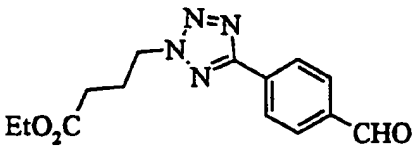
δ_H (300MHz, $CDCl_3$): 10.1 (1H, s), 8.35 (2H, d), 8.00 (2H, d), 4.98 (2H, t), 4.20 (2H, q), 3.16 (2H, t), 1.15 (3H, t).

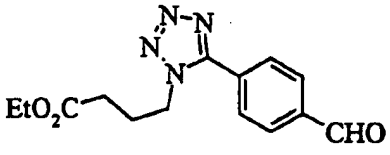
PREPARATIONS 70 and 71

Ethyl 4-[5-(4-formylphenyl)-2*H*-1,2,3,4-tetrazolyl-2-yl]butanoate

and

Ethyl 4-[5-(4-formylphenyl)-1*H*-1,2,3,4-tetrazolyl-2-yl]butanoate



and


A mixture of the compound of Preparation 42 (3g), potassium carbonate (5.9g) and methyl 4-bromobutanoate (4.68g) in dry acetonitrile (70ml) was heated together at 50°C for 16 hours. The reaction mixture was cooled to room temperature and evaporated to dryness *in vacuo*. The residue was partitioned between water and ethyl acetate, and the organic layer separated, dried (sodium sulphate) and evaporated *in vacuo*. The crude residue containing both N-1 and N-2 isomers was purified by column chromatography over silica gel (1/2 pentane/ethyl acetate) to afford the title compounds as a colourless oils. The N-2 isomer eluted first (3.9g):

R_f: 0.5 (1:2; ethyl acetate/pentane)

δ_H (300MHz, $CDCl_3$): 10.1 (1H, s), 8.33 (2H, d), 8.01 (2H, d), 4.79 (2H, t), 3.70 (3H, s), 2.50-2.35 (4H, m).

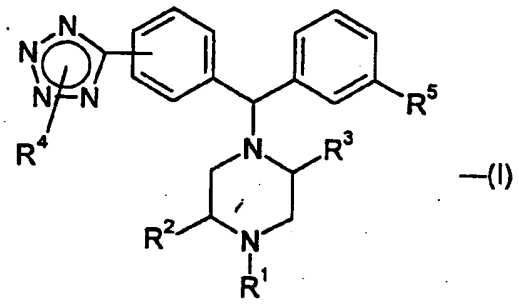
Followed by the N-1 isomer (0.35g)

R_f: 0.1 (1:2; ethyl acetate/pentane)

δ_H (300MHz, $CDCl_3$): 10.13 (1H, s), 8.10 (2H, d), 7.95 (2H, d), 4.58 (2H, t), 3.63 (3H, s), 2.42 (2H, t), 2.28 (2H, m).

CLAIMS

1. A compound of the formula:-



—(I)

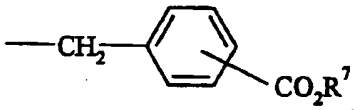
or a pharmaceutically acceptable salt thereof,

wherein

R^1 is H, C_2-C_6 alkanoyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, (C_3-C_7 cycloalkyl)-(C_1-C_4 alkyl), (C_1-C_4 alkoxy)-(C_1-C_4 alkyl), carboxy-(C_1-C_4 alkyl), aryl-(C_1-C_4 alkyl) or heteroaryl-(C_1-C_4 alkyl);

R^2 and R^3 are each independently H or C_1-C_4 alkyl;

R^4 is selected from (i) H, (ii) a group of the formula R^6-$(CH_2)_m$-Z-$(CH_2)_n$-, where m is 0, 1, 2 or 3, n is 1, 2 or 3, Z is a direct link or O, and R^6 is -CO_2H or -CO_2(C_1-C_4 alkyl), and (iii) a group of the formula



where R^7 is H or C_1-C_4 alkyl;

and R^5 is hydroxy, C_1-C_4 alkoxy or -$NHSO_2$(C_1-C_4 alkyl);

with the proviso that when Z is O, m is 1, 2 or 3 and n is 2 or 3.

2. A compound as claimed in claim 1, wherein (a) aryl is phenyl or naphthyl, both optionally substituted by up to three substituents each independently selected from halo, trifluoromethyl, C_1-C_4 alkyl and C_1-C_4 alkoxy, and (b) heteroaryl is a 5- or 6-membered aromatic heterocyclic group.

3. A compound as claimed in claim 2, wherein (a) aryl is phenyl optionally substituted by one or two substituents as defined in claim 2, and (b) heteroaryl is thiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl or pyrazolyl.

4. A compound as claimed in any one of the preceding claims, wherein R^1 is H, allyl, benzyl, C_1-C_4 alkyl or (C_3-C_7 cycloalkyl)methyl.

5. A compound as claimed in claim 4, wherein R^1 is allyl.

6. A compound as claimed in any one of the preceding claims, where R^2 and R^3 are preferably each independently H or CH_3.

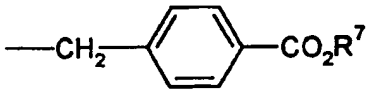
7. A compound as claimed in claim 6, wherein R^2 and R^3 are either both H or both methyl.

8. A compound as claimed in claim 7, wherein R^2 and R^3 are both methyl.

9. A compound as claimed in any one of the preceding claims, wherein R^5 is hydroxy, methoxy or $-NHSO_2Me$.

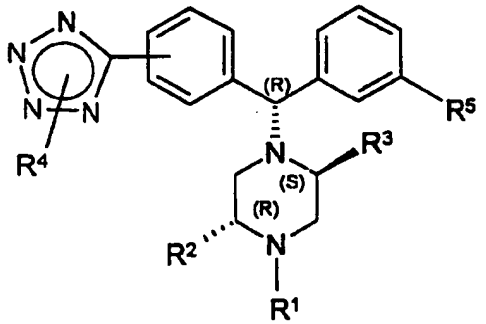
10. A compound as claimed in claim 9, wherein R^5 is hydroxy.

11. A compound as claimed in any one of the preceding claims wherein R^4 is H or a group of the formula (a) $-(CH_2)_pCO_2H$ or $-(CH_2)_pCO_2(C_1$-C_4 alkyl) wherein p is 1,2,3 or 4 (b) $-(CH_2)_2$-O-CH_2CO_2H (c) $-(CH_2)_2$-O-$CH_2CO_2(C_1$-C_4 alkyl) or (d)



where R^7 is H or C_1-C_4 alkyl.

12. A compound of the formula (I) as claimed in any one of the preceding claims which has the stereochemistry:-



---(IA)

13. A compound of the formula (I) as claimed in any one of the preceding claims in which the tetrazole ring is attached to the 3- or 4- position of the adjacent phenyl ring.

14. A compound of the formula (I) as claimed in claim 1 which is:-

(+)-5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole;

(-)-5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1H-tetrazole;

3-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)propionic acid;

(+)-5-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)valeric acid;

(+)-5-(5-{4-[(R)-α-(2(S),5(R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)valeric acid;

(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)-4-methylbenzoic acid;

(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)-4-methylbenzoic acid;

(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)-4-methylbenzoic acid;

(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-2-tetrazolyl)-4-methylbenzoic acid; or

(5-{4-[(R)-α-(2(S),5(R)-4-benzyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]phenyl}-1-tetrazolyl)-3-methylbenzoic acid.

15. A pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of the preceding claims and a pharmaceutically acceptable diluent or carrier.

16. A compound of the formula (I) or pharmaceutically acceptable salt thereof as claimed in any one of claims 1-14, for use as a medicament.

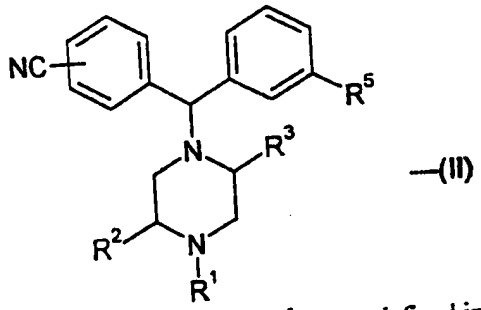
17. The use of a compound of the formula (I) or of a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-14 for the manufacture of a medicament for treating or preventing a disease requiring administration of a delta opioid agonist.

18. A method of treating or preventing a disease requiring administration of a delta opioid agonist, which comprises administering to a patient in need of such treatment an

effective amount of a compound of the formula (I) or pharmaceutically acceptable salt thereof as claimed in any one of claims 1-14.

19. A use or method as claimed in claim 17 or 18 respectively, wherein the disease is an inflammatory disease such as arthritis, psoriasis, asthma, or inflammatory bowel disease, a disorder of respiratory function, a gastro-intestinal disorder such as functional bowel disease, a functional GI disorder such as irritable bowel syndrome, functional diarrhoea, functional distension, functional pain, non-ulcerogenic dyspepsia or another associated with a disorder of motility or secretion, a urogenital disorder such as incontinence, or pain including non-somatic pain.

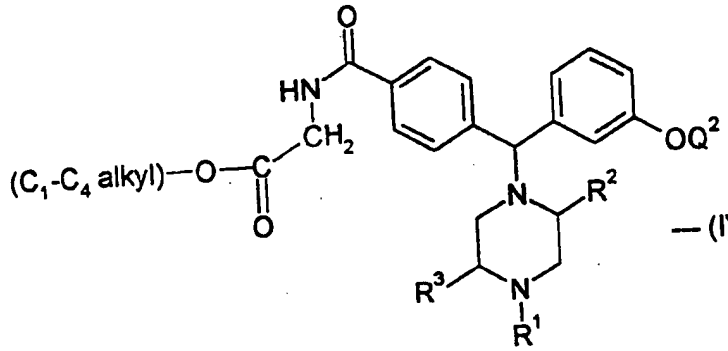
20. A compound of the formula:-



—(II)

wherein R^1,R^2,R^3 and R^5 are as defined in claim 1.

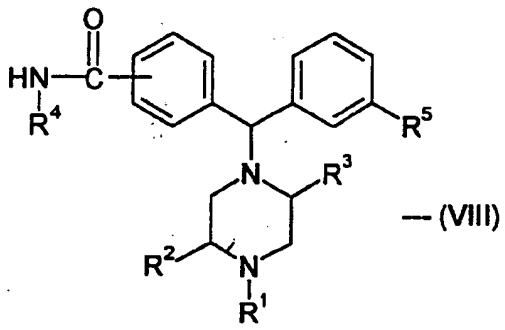
21. A compound of the formula:-



— (IV)

where R^1, R^2 and R^3 are as defined in claim 1 and Q^2 is a hydroxy-protecting group.

22. A compound of the formula:-



— (VIII)

wherein R^4 is R^6 –$(CH_2)_m$-Z-$(CH_2)_n$- and Z,m,n,R^1,R^2,R^3,R^5 and R^6 are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/EP 98/02277

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D257/04 C07D295/155 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 04051 A (THE WELLCOME FOUNDATION LTD.) 9 February 1995 see claims ---	1-22
A	WO 93 15062 A (THE WELLCOME FOUNDATION LTD.) 5 August 1993 see claims ---	1-22
A	US 3 453 285 A (S.H. ELKHART, IND.) 1 July 1969 see claims ---	1-22
A	EP 0 676 396 A (WAKAMOTO PHARM. CO., LTD.) 11 October 1995 see claims ---	1-22

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 1998	14/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/02277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 585 500 A (MERRELL DOW PHARM. INC.) 9 March 1994 see claims	1-22
P,X	WO 97 46240 A (DELTA PHARMACEUTICALS, INC.) 11 December 1997 see claims	20-22
P,X	WO 97 23466 A (ASTRA PHARMA INC.) 3 July 1997 see claims	20-22

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/02277

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18, 19
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 18, 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir. .ational Application No
PCT/EP 98/02277

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			WO	9405648 A	17-03-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/EP 98/02277

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 585500 A		ZA 9306362 A	28-03-1994
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